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Studies on the Control of Coronary Circulation
Part I. The Effect of the Stimulation of the Nerves on the Coronary Circulation. Part II. The Humoral Effect on the Coronary Circulation

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Part I. The Effect of the Stimulation of the Nerves on the Coronary Circulation

The nervous control of coronary circulation has long been studied, but many problems remain to be investigated further. In general, the coronary blood flow increases by sympathetic nerve stimulation, and decreases by vagal nerve stimulation.[1-7] But, the stimulation of the sympathetic or vagal nerve to the heart produces significant changes in hemodynamic and metabolic factors, such as blood pressure, heart rate, vigor of contraction, ratio of systole to diastole, cardiac output, extravascular compression, massaging action of the heart, oxygen consumption, and metabolites.[8-16] Therefore, it cannot be concluded simply that the sympathetic nerve causes active coronary vasodilatation, while the vagal nerve causes active coronary vasoconstriction.

The effects of the stimulation of the proximal or peripheral end of the vagal nerves and stellate ganglia upon the coronary circulation are reported in the present paper. The relationships between vasomotor, hemodynamic, and metabolic factors in the coronary circulation are studied.

METHODS AND PROCEDURES

Thirty-three dogs weighing 10 to 15 kilograms were anesthetized with sodium thiopental, 0.03 to 0.05 Gm. per kilogram, intravenously. Under artificial respiration the left side of the

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chest was partially opened between the third and fifth ribs. As shown in Fig. 1, the arterial blood was led out from the right femoral artery through a vinyl tube. Then, a specially designed cannula was inserted into the ostium of the left coronary artery, through which the arterial blood from the vinyl tube was allowed to flow into the left coronary artery. Thus, a self-perfusing system to the left coronary artery was established.

The left coronary blood flow was measured with a Shipley recording rotameter.[16] The blood pressure was measured with a mercury manometer from the left femoral artery, and partially with a Sanborn electromanometer placed between the rotameter and the coronary artery.

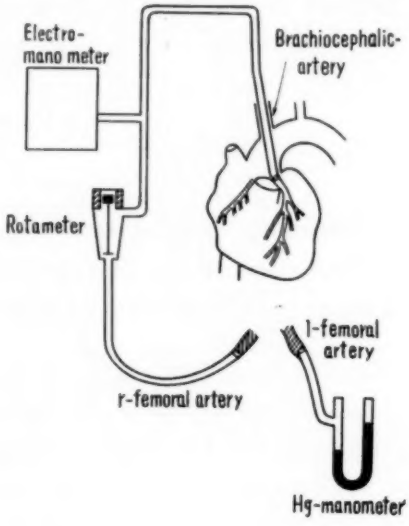

Fig. 1.—Schematic diagram of the experimental arrangement.

The mean blood pressure was calculated from the formula

$$\overline{BP} = DBP + 1/3\ PP$$

where $\overline{BP}$ = mean blood pressure, DBP = diastolic blood pressure, and PP = pulse pressure. The calculated peripheral resistance in the coronary vascular bed was measured from the relationship

$$CVR = \overline{BP}/CBF$$

where CVR = coronary vascular resistance, $\overline{BP}$ = mean blood pressure, and CBF = coronary blood flow.[16]

The left and/or right vagosympathetic trunks were isolated in the neck. In addition, the left and/or right stellate ganglia with their respective cardiac branches were isolated for the purpose of the experiments.

The electrical stimulation of the nerve was carried out with a spiky wave produced by a thyratron. The stimulation was continued for 10 to 15 seconds, with a frequency of 15 to 30 cycles per second and an intensity of 0.5 to 30 volts. Heparin (10 mg. per kilogram) was given intravenously as an anticoagulant.

RESULTS

A. *Stimulation of the Proximal End of the Cut Vagal Nerve.*—In 26 experiments on 9 dogs the proximal ends of the cut vagal nerves were electrically stimulated (10 to 15 seconds) on the left side, and in 14 experiments on 5 dogs, on the

right side. During the stimulation the blood pressure was elevated (pressor response) or depressed (depressor response), and sometimes it was elevated initially and then depressed (pressor-depressor response).

Out of a total of 40 experiments on 11 dogs, pressor responses occurred in 8 experiments on 5 dogs; pressor-depressor responses occurred in 16 experiments on 8 dogs; depressor responses occurred in 14 experiments on 6 dogs; and depressor-pressor responses occurred in 2 experiments on 2 dogs.

Coronary blood flow increased in pressor responses, decreased in depressor responses, and first increased and thereafter decreased in pressor-depressor responses.

Fig. 2 is a record of the experiment in which the pressor response occurred. In this experiment the mean blood pressure was elevated from 74 to 105 mm. Hg during the stimulation, and then fell progressively to the control value. The heart rate was unchanged. The left coronary blood flow increased from 51 to 115 c.c. per minute, and the calculated coronary vascular resistance decreased from 1.47 to 0.92.

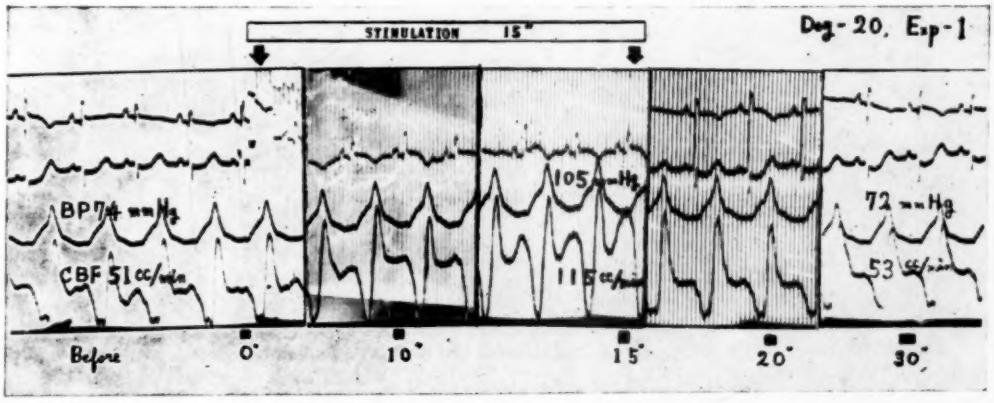

Fig. 2.—A record showing changes in coronary blood flow and blood pressure in the pressor response produced by the stimulation of the proximal end of the cut vagal nerve. The ECG was recorded in Leads I and II.

Key to abbreviations in this and all subsequent illustrations: C.B.F. = Coronary blood flow (c.c./min.). B.P. = Mean blood pressure (mm. Hg). H.R. = Heart rate.

In all the other experiments in which the blood pressures were elevated, the coronary blood flow also increased, either in pressor responses (8 experiments) or in the pressor phases of pressor-depressor responses (16 experiments). The calculated coronary vascular resistance decreased when the coronary blood flow increased maximally during the peak of the blood pressure, with the exception of 5 experiments. The heart rates were unchanged, or only slightly changed in these experiments.

The relationship between the elevation of the mean blood pressure and the change in the coronary vascular resistance is shown in Fig. 3. It seems likely that the greater the elevation of the mean blood pressure the greater the decrease in coronary vascular resistance.

In Fig. 4 an experiment with the depressor response is demonstrated. In this experiment the mean blood pressure fell progressively from 70 to 40 mm. Hg, and the coronary blood flow decreased from 74 to 38 c.c. per minute. The calculated coronary vascular resistance increased from 0.95 to 1.05.

In all the other experiments in which the blood pressures were depressed, the coronary blood flow also decreased, either in depressor responses (14 experiments) or in the depressor phases of pressor-depressor responses (14 experiments). With the exception of 7 experiments, the calculated coronary vascular resistance increased when the coronary blood flow decreased during the maximal fall in the blood pressure. The heart rates were either unchanged or slightly decreased (slight bradycardia) in these experiments.

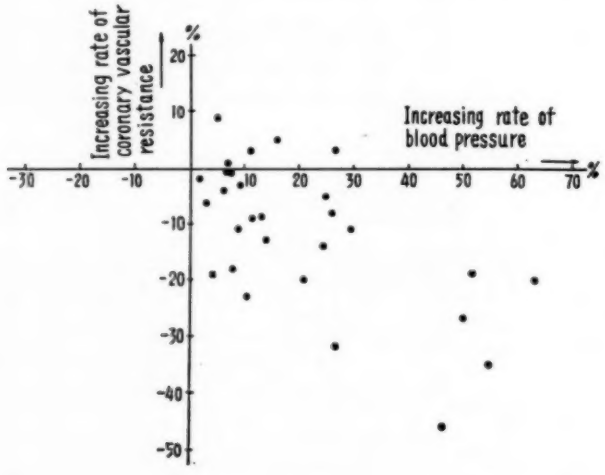

Fig. 3.—The relationship between coronary vascular resistance and blood pressure in cases with pressor response produced by the stimulation of the proximal end of the cut vagal nerve.

The relationship between the depression of the mean blood pressure and the increase in the coronary vascular resistance is shown in Fig. 5. But there is no quantitative relationship between the two variables.

These experiments were performed with various combinations of the vagal or sympathetic nerve sections (one or both vagosympathetic trunks and one or both stellate ganglia); in addition, either the left or right vagal nerve (proximal end) was stimulated. Responses of the blood pressure, coronary blood flow, and coronary vascular resistance, however, were essentially the same between the various groups.

B. *Stimulation of the Sympathetic Nerve.*—The isolated stellate ganglia with their cardiac branches were stimulated electrically for 15 seconds, on the left side in 32 experiments on 14 dogs, and on the right side in 21 experiments on 7 dogs.

A typical experiment of the stimulation of the left sympathetic nerve is shown in Fig. 6. The mean blood pressure was elevated from 70 to 82 mm. Hg during the stimulation, and then was slowly elevated again after the stimulation.

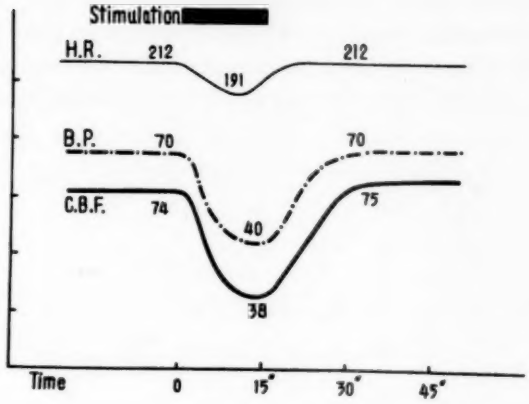

Fig. 4.—A schematic representation showing changes in coronary blood flow, blood pressure, and heart rate, in the depressor response produced by the stimulation of the proximal end of the cut vagal nerve.

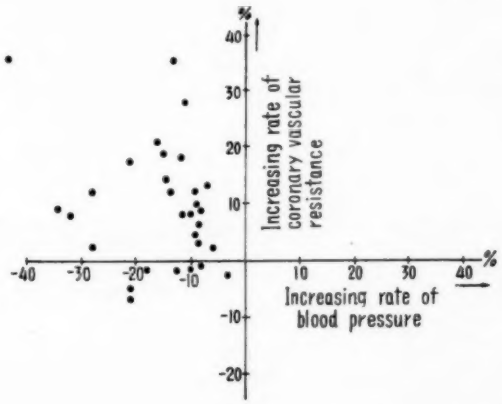

Fig. 5.—The relationship between coronary vascular resistance and blood pressure in cases with depressor response produced by the stimulation of the proximal end of the cut vagal nerve.

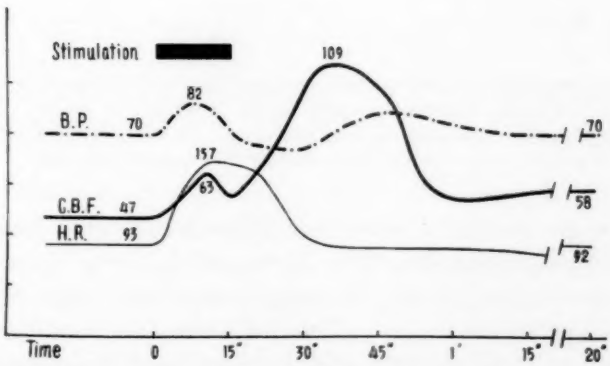

Fig. 6.—A schematic representation showing changes in coronary blood flow, blood pressure, and heart rate, produced by the stimulation of the left sympathetic nerve.

The latter elevation of the blood pressure persisted for a long time and was due probably to the neurohumoral effects. The coronary blood flow initially increased from 47 to 63 c.c. per minute (initial response of the coronary blood flow) and somewhat decreased parallel to the change of the blood pressure, and then

Fig. 7.

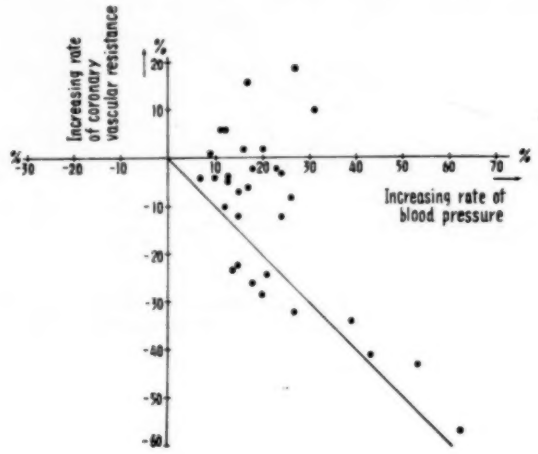

Fig. 8.

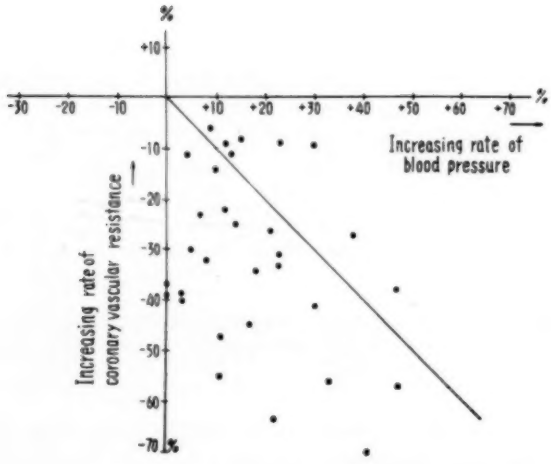

Fig. 7.—The relationship between coronary vascular resistance and blood pressure in the initial responses produced by the stimulation of the left sympathetic nerve.

Fig. 8.—The relationship between coronary vascular resistance and blood pressure in the late responses produced by the stimulation of the left sympathetic nerve.

greatly increased again to 109 c.c. per minute (late response of the coronary blood flow which persisted for approximately 45 seconds). The heart rate increased from 93 to 157 per minute during the stimulation, and then progressively returned to the control value. The calculated coronary vascular resistance decreased from 1.49 to 1.30 during the initial response of the coronary blood flow, and further decreased markedly to 0.79 during the late response of the coronary blood flow.

In the other experiments of stimulation of the left sympathetic nerve the responses of the blood pressure, coronary blood flow, and coronary vascular resistance were essentially the same as in the experiment shown in Fig. 6. That is, the blood pressure was elevated initially during the stimulation, and, in the majority of the cases, it was elevated again, probably because of the neurohumoral effects (to a lesser degree of elevation, but of longer duration than initially).

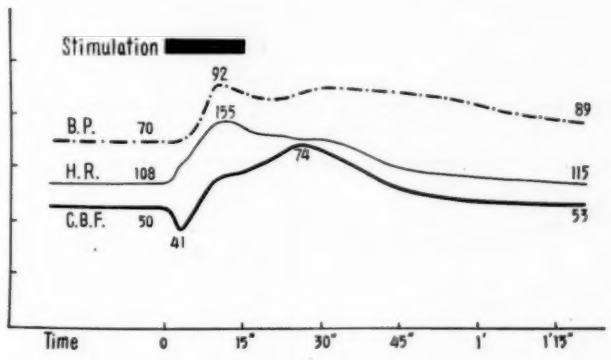

Fig. 9.—A schematic representation showing changes in coronary blood flow, blood pressure, and heart rate in the case with initial decrease in coronary blood flow, produced by the stimulation of the sympathetic nerve.

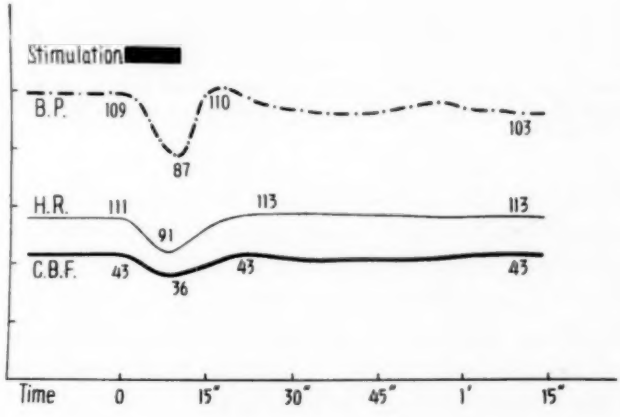

Fig. 10.—A schematic representation showing changes in coronary blood flow, blood pressure, and heart rate, produced by the stimulation of the vagal nerve.

The coronary blood flow increased with the initial elevation of the blood pressure (initial response of coronary blood flow) and then increased more markedly with, or sometimes nearly without, elevation of the blood pressure (late response of coronary blood flow). The late response of coronary blood flow persisted for a longer time than the initial response, sometimes over 1 or 2 minutes. The calculated coronary vascular resistance decreased during the initial responses of coronary blood flow, and was still further greatly decreased in the late responses of coronary blood flow.

The relationships between the elevation of the mean blood pressure and the decrease in coronary vascular resistance are shown in Figs. 7 and 8. The decreases in coronary vascular resistance during the initial responses of coronary blood flow (Fig. 7) resemble those of the pressor responses produced by the stimulation of the proximal end of the cut vagal nerves (Fig. 3). In contrast, the decreases in coronary vascular resistance during the late response of coronary blood flow (Fig. 8) are markedly greater than those of the initial responses, regardless of the degree of elevation of the mean blood pressure.

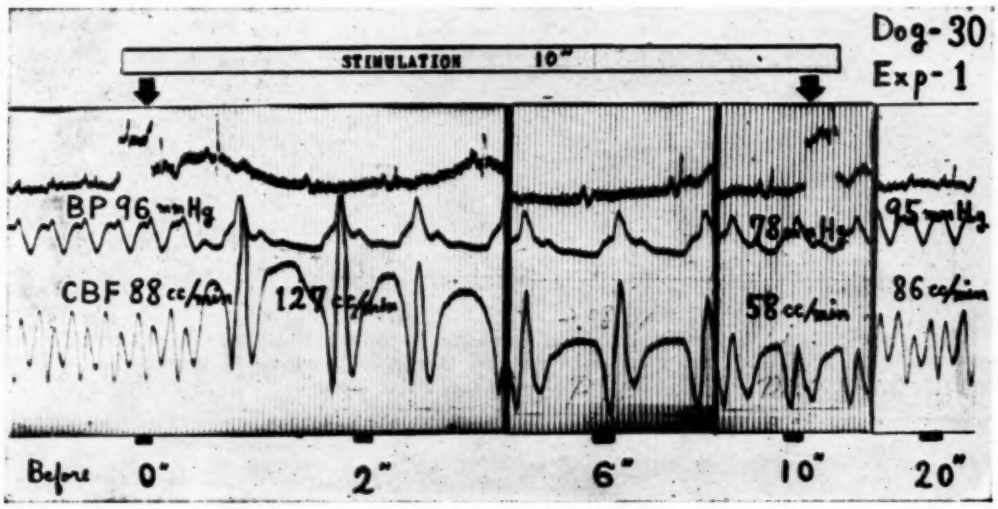

Fig. 11.—A record showing changes in coronary blood flow and blood pressure in the case with initial increase in coronary blood flow, produced by stimulation of the right vagal nerve. The ECG was recorded in Lead II.

Stimulation of the right sympathetic nerve produced the "initial" and "late" responses, also, and the decreases in coronary vascular resistance during the late responses were likewise much greater than those of the initial responses, as in the stimulation of the left sympathetic nerve.

Various degrees of tachycardia occurred in almost all these experiments, but no relationship could be found between the increase in heart rate and the coronary blood flow, or the coronary vascular resistance.

In the experiment shown in Fig. 9 the coronary blood flow decreased from 50 to 41 c.c. per minute, while the blood pressure was unchanged. The heart rate increased slightly from 108 to 119 per minute. The initial decreases in coronary blood flow, as shown in Fig. 9, were also observed in 12 experiments on 5 dogs, from among a total of 53 experiments on 15 dogs. During these phases of the decrease in coronary blood flow, the blood pressure was depressed in 5 experiments on 2 dogs, while it was either slightly elevated or unchanged in 7 experiments on 4 dogs. The incubation time of these initial decreases in coronary blood flow ranged from 1.5 to 3.5 seconds (an average of 2.3 seconds); the duration of these decreases in coronary blood flow ranged from 2.5 to 10 seconds (an average of 4.5 seconds). An increase of from 4 to 55 per cent in heart rates

was observed during these phases of decrease in coronary blood flow. In 7 experiments in which the coronary blood flow decreased without depression of the blood pressure, however, the tachycardias were generally slight, except in one experiment.

C. *Stimulation of the Peripheral End of Vagal Nerve.*—The peripheral ends of the cut vagal nerves were electrically stimulated for 10 seconds, on the left side in 15 experiments on 11 dogs, and on the right side in 4 experiments on 4 dogs.

During the stimulation of the vagal nerve the depression of the blood pressure and bradycardia occurred in all experiments. In an experiment shown in Fig. 10 the mean blood pressure fell from 109 to 87 mm. Hg; the heart rate de-

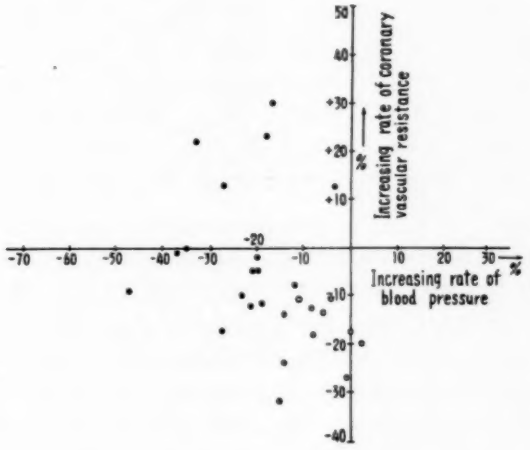

Fig. 12.

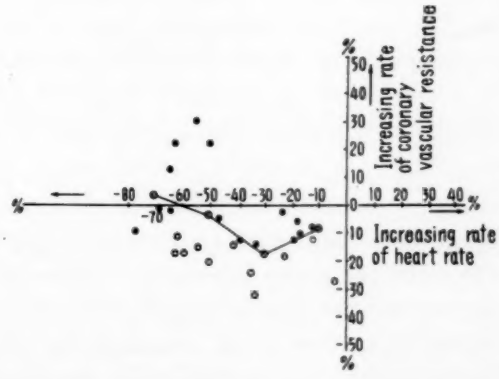

Fig. 13.

Fig. 12.—The relationship between coronary vascular resistance and blood pressure in the phases of decreased coronary blood flow (black dots) and in the initial phases with increase in coronary blood flow (white dots), produced by the stimulation of the vagal nerve.

Fig. 13.—The relationship between changes in coronary vascular resistance and heart rate, produced by the stimulation of the vagal nerve. Black dots = in the phases of decreased coronary blood flow; white dots = in the initial phases with increase in coronary blood flow; black dots within circle = average values of four groups in which the decrease in heart rate ranged from 0 to 20 per cent, over 20 per cent, over 40 per cent, and over 60 per cent, respectively.

creased from 111 to 91 per minute, and the coronary blood flow decreased from 43 to 36 c.c. per minute. The calculated coronary vascular resistance decreased very slightly from 2.54 to 2.42.

In contrast, in another experiment, shown in Fig. 11, the coronary blood flow increased initially from 88 to 127 c.c. per minute, with marked bradycardia, and then decreased to 58 c.c. per minute with the depression of the blood pressure.

The initial increases in coronary blood flow, as shown in Fig. 11, occurred in 10 experiments on 9 dogs. There were 3 experiments in which only the increase in coronary blood flow was observed, with no definite phase of the decrease noted. Of these 10 experiments the blood pressure was depressed in 6 and nearly unchanged in 4.

Changes in coronary vascular resistance during stimulation of the vagal nerve were quite different from those of the "depressor" responses produced by stimulation of the proximal ends of the vagal nerves. As shown in Fig. 12, the calculated coronary vascular resistance decreased markedly during phases of the initial increase in coronary blood flow. Moreover, it decreased also during phases of the decrease in coronary blood flow, in 10 out of 16 experiments. In contrast, in the majority of the "depressor" responses the coronary vascular resistance increased, as shown in Fig. 5.

Generally, marked bradycardia occurred during stimulation of the vagal nerve, while changes in heart rate were only slight in the "depressor" responses. Thus, it is an interesting question as to whether the bradycardia has any direct influence on the coronary blood flow. The relationship between the bradycardia and the coronary vascular resistance is shown in Fig. 13. It seems likely that the more the heart rate decreases the more the coronary vascular resistance decreases, when the degree of the bradycardia is not over approximately 40 per cent. In marked bradycardia (over approximately 40 per cent) the coronary vascular resistance tended to increase. But the initial increase in coronary blood flow (white dots in Fig. 13) occurred with either very slight or marked bradycardia, in spite of depression of the blood pressure. Therefore, the increase in coronary blood flow or the decrease in coronary vascular resistance may result not only from the bradycardia but also from the other factors.

DISCUSSION

A. *Stimulation of the Proximal End of the Cut Vagal Nerve.*—The stimulation of the proximal ends of the vagal nerves was followed by either elevation (pressor response) or depression (depressor response) of the blood pressure. The coronary blood flow increased or decreased, respectively, parallel to changes in blood pressure. The existence of any nervous reflex mechanism to the coronary vascular bed could not be proved in these experiments, as already described, and, therefore, changes in the coronary blood flow were assumed to be due chiefly to changes in the blood pressure (heart rates were unchanged or only slightly changed).

The finding that the coronary blood flow increases with the elevation of the blood pressure has been widely supported by many investigators. But, as to a

so-called pressure-flow relationship, no agreement has been reached. Recently, Eckenhoff[10] observed a close relationship of coronary blood flow to blood pressure. Katz[17] reported that the effective perfusion pressure (aortic minus coronary venous pressure) was a direct determinant of the coronary blood flow. Osher[18] has claimed that the logarithm of the coronary blood flow or the arterial blood pressure was a linear function of the other.

No simple relationship between the mean blood pressure and coronary blood flow could be observed in our experiments reported in this paper. But the calculated coronary vascular resistance decreased in pressor responses, while it increased in depressor responses. That is, either in pressor responses or depressor responses the degree of changes in coronary blood flow is greater than that of changes in mean blood pressure.

Wiggers[19] has reported that the coronary vascular resistance decreased with the elevation of the blood pressure by compression of the aorta; in contrast, it increased with the elevation of the blood pressure by epinephrine. He attributed this increase either to the passive dilatation of the coronary vessels by higher blood pressure or to the local vasorelaxation by release of metabolites. The influence of myocardial oxygen consumption on the coronary blood flow, more effective than that of the blood pressure, has been reported by Eckenhoff[20] and Alella[21] and their associates. In addition, Osher[18] and Wiggers[19] have emphasized consideration of the so-called massaging action of the heart.

From the results reported in this paper it can be deduced that the decreases in coronary vascular resistance in pressor responses are due mostly to the elevation of the blood pressure. This means that the decrease in coronary vascular resistance is regarded as the summated effects of the elevation of the blood pressure itself and the accompanying changes in several factors, such as oxygen consumption, metabolites, myocardial compression, massaging action of the heart, passive vasodilatation, heart rate, cardiac output, etc. Therefore, if one includes all the effects mentioned above, it can be concluded that the elevation of the blood pressure reduces the coronary vascular resistance. In the same manner, it may be concluded that the depression of the blood pressure produces the increase in coronary vascular resistance.

B. *Stimulation of the Sympathetic Nerve.*—Stimulation of the stellate ganglion produced an elevation of the blood pressure, an increase in cardiac vigor, and tachycardia. During stimulation the coronary blood flow increased initially with elevation of the blood pressure ("initial response" of coronary blood flow), and again greatly increased with or without the elevation of the blood pressure ("late response" of coronary blood flow). The late response of the coronary blood flow often persisted over 1 or 2 minutes. Sometimes the coronary blood flow decreased early during the stimulation, just before the "initial response" ("initial decrease" in coronary blood flow).

The calculated coronary vascular resistance decreased in the initial response and decreased still more significantly in the late response. The decrease in coronary vascular resistance in the "initial response" resembles that in the "pressor response" produced by the stimulation of the proximal end of the vagal nerve. Therefore, both the increase in coronary blood flow and the decrease in coronary

vascular resistance in the "initial response" may be due to the elevation of the blood pressure. In contrast, the great decrease in coronary vascular resistance in the "late response" may be supposed to be due to the active vasodilatation.

The existence of coronary vasodilatative substances in the coronary sinus blood, either during or immediately after stimulation of the sympathetic nerve, will be reported in the next part of this paper. By comparison of the effects upon the coronary vessels of such coronary sinus blood with those of norepinephrine it is at present thought that these substances are metabolites rather than neurohumoral substances. This belief may support the deduction that the "late response" in coronary blood flow is mostly attributed to the change in myocardial metabolism.

Past investigations have indicated that the coronary blood flow increased by stimulation of the sympathetic nerve.[16] The increase in coronary blood flow has been attributed to active vasodilatation by many investigators, for example, by Gregg and Shipley,[8] Eckenhoff and associates,[10] Winbury and Green,[15] Eckstein and associates.[13] The mechanism of the active vasodilatation remains to be determined, but changes in myocardial metabolism (metabolites, oxygen consumption) have been regarded as more important than direct vasodilatation by the nervous control of the coronary vessels.

Initial decreases in coronary blood flow with either elevation or no change in the blood pressure were observed in 7 experiments out of a total of 53. The decrease in coronary blood flow without depression of the blood pressure appeared promptly after the beginning of the stimulation. Therefore, the decrease in coronary blood flow may be due either to direct vasoconstriction by sympathetic nervous control of the coronary vessels or to passive vasoconstriction by extravascular compression. But the decrease in coronary blood flow cannot always be observed, because of the immediate elevation of the blood pressure which causes the increase in coronary blood flow.

In the next part of this paper it will be reported that with the intracoronary injection of norepinephrine the coronary blood flow often initially decreases with no change in blood pressure. Lu and Melville[23] have explained that the initial decrease in coronary blood flow produced by norepinephrine was due to the myocardial compression to the coronary vascular bed. On the other hand, Katz and Jochim[22] concluded, however, that the sympathetic nerve carried coronary vasoconstrictor fibers, from observations that stimulation of the sympathetic nerve occasionally reduced the coronary blood flow in the fibrillating heart perfused at constant pressure.

Thus, it can be concluded that by stimulation of the sympathetic nerve the coronary blood flow initially increases parallel to the elevation of the blood pressure (initial response of coronary blood flow), and that it then increases more markedly, probably because of changes in myocardial metabolism (late response of coronary blood flow). Sometimes the coronary blood flow decreases early during the stimulation, probably because of active vasoconstriction of the nervous system or because of the extravascular compression.

C. *Stimulation of the Peripheral End of the Vagal Nerve.*—Stimulations of the peripheral ends of the cut vagal nerves were followed by the depression of

the blood pressure and bradycardia. The coronary blood flow decreased parallel to the depression of the blood pressure. But in about half of the experiments the coronary blood flow increased initially with or without depression of the blood pressure. The calculated coronary vascular resistance markedly decreased in the initial phases with increased coronary blood flow; moreover, it often decreased in the phases of decreased coronary blood flow. These increases in coronary blood flow or decreases in the coronary vascular resistance are quite different from those in the depressor responses discussed in section A.

Anrep[2] has reported that the stimulation of the peripheral ends of the cut vagal nerve produced active vasoconstriction, and thereby reduced the coronary blood flow. The coronary vasoconstriction via the vagal nerve has been suggested by many investigators, such as Hochrein,[3] Rein,[4] and Essex[7] and their associates. However, Winbury[15] and Eckenhoff[10,14] and associates have attributed the decrease in coronary blood flow accompanying stimulation of the vagal nerve only to the depression of the blood pressure. Eckenhoff has claimed that no appreciable vasoconstriction was induced by stimulation of the vagal nerve.

In contrast to the investigations mentioned above, Klisiecki and Flek[24] reported that the coronary blood flow was increased slightly by stimulation of the vagal nerve, so far as changes in blood pressure and heart rate were not significant. Both Katz and Jochim,[22] in the fibrillating heart under constant pressure perfusion, and Heidenreich and Schmidt,[25] in cross circulation, have claimed that the coronary blood flow increased because of the active vasodilatation induced by stimulation of the vagal nerve.

Bradycardia may have some relation to the decrease in coronary vascular resistance (see Fig. 13). But the initial increases in coronary blood flow with short incubation times can be attributed to the active vasodilatation brought on by stimulation of the vagal nerve, because it has been observed irrespective of the degree of bradycardia and even in spite of depression of the blood pressure.

It may be concluded that stimulation of the vagal nerve produces the coronary vasodilatation and the initial increases in coronary blood flow; however, the coronary blood flow decreases thereafter, or throughout the stimulation from the beginning, because of the marked depression of the blood pressure; the bradycardia may have some vasodilatative effects.

SUMMARY

Nervous control of the coronary circulation was studied in the dog's heart, beating in situ under a self-perfusing system. Coronary blood flow was measured with a rotameter.

1. Stimulation of the proximal ends of the vagal nerves were followed by either pressor or depressor responses. In pressor responses the coronary blood flow increased and the coronary vascular resistance decreased, while in depressor responses the coronary blood flow decreased and the coronary vascular resistance increased.

It is supposed that changes in coronary vascular resistance in either pressor or depressor responses resulted passively from the hemodynamic factors, chiefly because of changes in blood pressure.

2. With stimulation of the sympathetic nerve the coronary blood flow increased initially parallel to the elevation of the bood pressure (initial response), and then, again increased further more markedly with or without elevation of the blood pressure (late response). The decrease in coronary vascular resistance in the "initial response" may be due to the passive vasodilatation resulting from hemodynamic factors (elevation of the blood pressure), while in the "late response" it may be due to the active vasodilatation resulting from metabolic factors (metabolites and oxygen consumption). Sometimes the initial decreases in coronary blood flow were observed with or without elevation of the blood pressure.

It can be deduced that stimulation of the sympathetic nerve may often produce (at least, initially) coronary vasoconstriction, actively by the nervous pathways to the coronary vessels, or passively by the extravascular compression of the myocardium.

3. With stimulation of the peripheral end of the vagal nerve the coronary blood flow generally decreased, as a result of depression of the blood pressure. But in about half of the experiments the initial increases in coronary blood flow were observed with or without depression of the blood pressure. The coronary vascular resistance markedly decreased during the initial increase in coronary blood flow; in addition, it decreased also in the phases of decreased coronary blood flow, in over half of the experiments.

It may be concluded that these vasodilatative actions are due to the active vasodilatation by the vagal nervous pathways, and somewhat to the bradycardia.

Part II. The Humoral Effect on the Coronary Circulation

The action of the sympathetic nerve on the coronary vessels is a very interesting and mysterious problem. Although many investigators observed that the coronary blood flow was markedly increased following the stimulation of the stellate ganglia or their cardiac branches,[8,9,15] it cannot be concluded that the sympathetic nerves dilate coronary vessels directly. In those instances of increase in coronary blood flow after stimulation the increase is almost always associated with elevation of blood pressure and an increase in heart rate, vigor of contraction, and cardiac output, as well as metabolic changes of the heart. Since these hemodynamic and metabolic changes induce an increase in coronary blood flow, it is very difficult to study the direct action of the sympathetic nerve on the coronary vessels.

Many authors[1,2,26,27] believe in the presence of the sympathetic coronary vasodilators, but we cannot agree with them at present. In the preceding studies of our present report we have discussed and proved the effects of hemodynamic changes on the coronary flow, and have suggested that the direct action of the sympathetic nerve on the coronary vessels was vasoconstrictive, and that the coronary vasodilatation following the stimulation of the sympathetic nerve might result from the hemodynamic and metabolic changes. It is generally suspected that the metabolites of the heart, released following the sympathetic stimulation,

may increase the coronary blood flow. It is the purpose of this study to demonstrate the presence of vasodilatative substances in coronary venous blood, and to clarify the nature of the sympathetic coronary vasodilatative effect, comparing the action of these substances with that of certain drugs on the coronary vessels.

MATERIALS AND METHODS

Young dogs with open chest and artificial respiration, ranging in weight from 10 to 15 kilograms, were used under sodium thiopental anesthesia (20 to 30 mg. per kilogram). By careful dissection, the stellate ganglia and their cardiac branches were exposed. Then, 10 mg. per kilogram of heparin sodium was injected as an anticoagulant, and the left coronary artery was perfused from the right femoral artery. A glass cannula was inserted into the orifice of the left coronary artery via the right subclavian artery. Coronary inflow was measured by a rotameter inserted between the cannula in the right femoral artery and that in the coronary artery. The blood pressure of the left femoral artery was measured with a mercury manometer (Fig. 14).

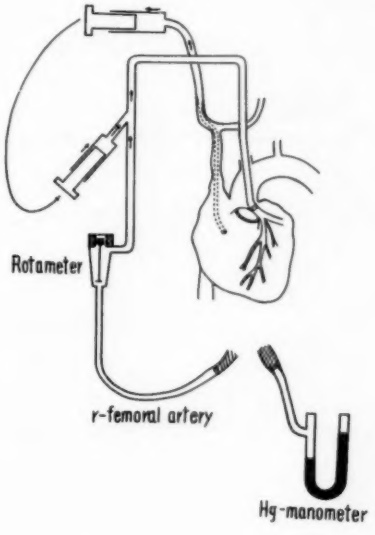

Fig. 14.—Schematic diagram of the experimental arrangement.

1. The peripheral ends of the cut stellate ganglia or their cardiac branches were stimulated electrically, and the coronary venous blood was drawn into the syringes through a catheter inserted into the coronary sinus via the right jugular vein. In one experiment the blood samples were obtained six times, that is, before and during stimulation of the sympathetic nerves and after stimulation, at 15 seconds, 1 minute, 2 minutes, and 3 minutes. Then, within 10 seconds, 1 c.c. of these blood samples was immediately injected into the tube leading to the coronary artery from the rotameter, and the changes induced in coronary blood flow were investigated. In some experiments the blood was immediately centrifuged, and the plasma obtained was injected.

2. The peripheral ends of the cut cervical vagal nerves were stimulated electrically, and the blood samples were obtained from the coronary sinus according to the procedure described above. Then, the samples were injected into the tubing within 10 seconds.

3. One cubic centimeter of 0.85 per cent saline solution, 0.01 μg/c.c. to 10 μg/c.c. of norepinephrine solution, 0.01 μg/c.c. to 10 μg/c.c. of acetylcholine solution, and 1 μg/c.c. to 1 mg./c.c. of adenosine triphosphate (ATP) solution were injected into the tubing within 10 seconds. Norepinephrine, acetylcholine, and ATP were dissolved in 0.85 per cent saline solution.

RESULTS

1. Coronary blood flow was markedly increased by the injection of the blood samples which had been obtained during the stimulation of the sympathetic nerves or 15 seconds after such stimulation. Fig. 15 shows a typical case in which the blood sample obtained 15 seconds after the end of sympathetic stimulation was injected. In such cases the increase in coronary blood flow was observed immediately after the injection, and lasted for 10 to 20 seconds or a little longer. No changes of blood pressure and heart rate were observed. On the other hand, the injection of the blood samples which had been obtained before the stimulation, or those obtained 1 minute or more after stimulation, did not induce such a marked augmentation of the coronary blood flow (Fig. 16). These findings were observed in more than half of our total experiments (Fig. 17). The injection of the blood samples obtained in the experiments on vagal stimulation was not followed by marked augmentation of the coronary blood flow (Fig. 18).

Fig. 15.

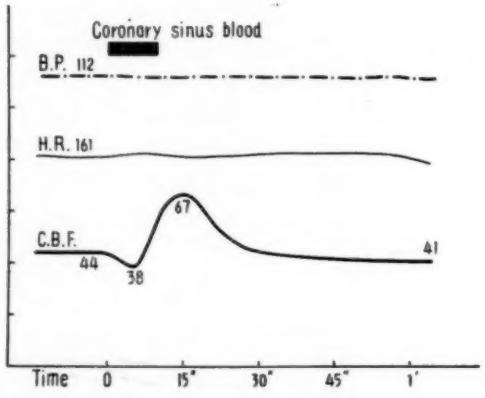

Fig. 16.

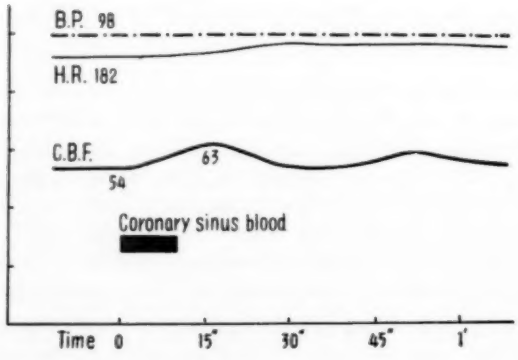

Fig. 15.—Intracoronary artery injection of a coronary venous blood sample obtained 15 seconds after the end of sympathetic stimulation. Coronary blood flow is increased markedly without any remarkable changes of blood pressure and heart rate.

Fig. 16.—Intracoronary artery injection of a blood sample obtained before the stimulation of the stellate ganglion. Increase in coronary blood flow is not so marked as in Fig. 15.

2. Saline solution, 0.85 per cent, did not cause any marked increase in coronary blood flow. In some cases the increasing rate of the coronary blood flow reached 10 per cent or a little more, but was never more than 20 per cent.

3. More than 0.01 μg of norepinephrine increased the coronary blood flow. In these instances the patterns of coronary blood flow were very characteristic. The coronary blood flow was increased slowly after the end of the injection, and the duration of the increase in flow was longer. It often lasted for several minutes. The increase in coronary blood flow was always associated with elevation of blood pressure and increase in heart rate. When large doses of norepinephrine were given, initial decrease in coronary blood flow preceded the late marked increase. It seems that the typical pattern of coronary blood flow induced by intracoronary artery injection of norepinephrine is similar to that following the sympathetic stimulation.

4. Injections of small doses of acetylcholine often increased the coronary blood flow without any remarkable change in blood pressure or heart rate. Large doses of acetylcholine (10μg/c.c. or larger) decreased heart rate and blood pres-

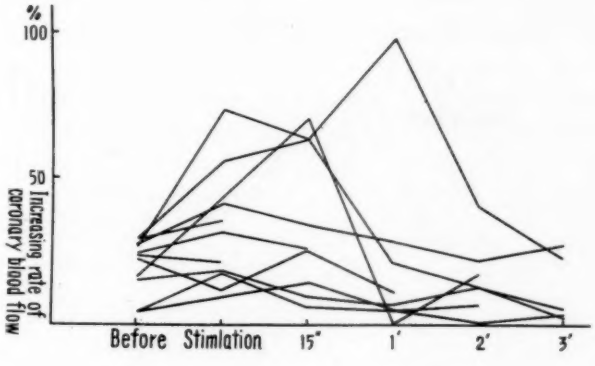

Fig. 17.

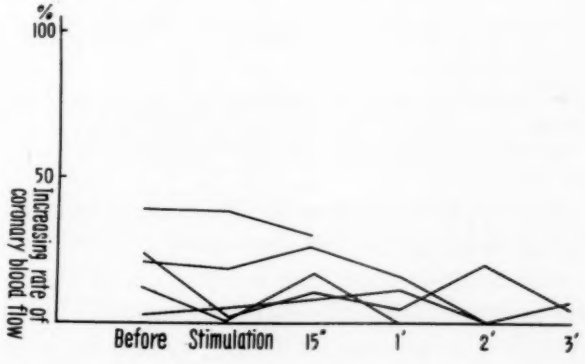

Fig. 18.

Fig. 17.—Increasing rate of coronary blood flow following the intracoronary artery injection of the coronary venous blood samples obtained before, during, and after sympathetic stimulation. Marked increase in coronary blood flow was observed after the injection of the blood samples obtained during, or 15 seconds after, the stimulation of the sympathetic nerves.

Fig. 18.—Increasing rate of coronary blood flow following the intracoronary artery injection of blood samples obtained before, during, and after the vagal stimulation.

sure. In these cases the decrease in heart rate almost always resulted from A-V block. When the blood pressure fell markedly, the decrease in coronary blood flow followed the initial increase.

5. More than 1 μg of ATP increased the coronary blood flow. In those instances no remarkable changes in heart rate were observed. The injection of large doses of ATP was followed by a marked increase in coronary blood flow, in spite of a slight decrease in blood pressure. The effects of acetylcholine and ATP on coronary blood flow appeared rapidly and lasted for 15 to 30 seconds or less.

DISCUSSION

It is generally accepted that the chemical materials of the blood and tissue fluids within the heart are of great importance in determining the volume of coronary blood flow, and many workers have studied the coronary blood flow in relation to metabolism and work of the heart.[9,10,12,21] It has been supposed that coronary vasodilatation may result from an increased local production of metabolites released within the heart. Eckstein and associates[28] have studied the coronary dilatative effect of coronary venous blood, but could not demonstrate the presence of any vasodilatative substance in it.

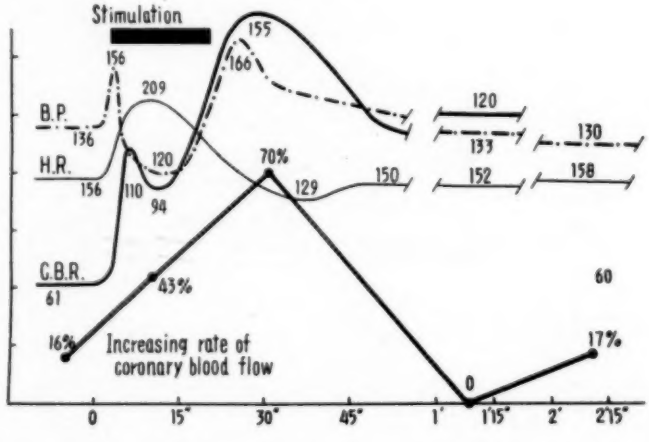

Fig. 19.—Relationship between the coronary blood flow pattern and the increasing rate of coronary blood flow following the injection of each coronary venous blood sample. The effective blood samples were obtained during the time corresponding to the increased responses. (See text.)

From our present experiments it is obvious that a marked augmentation of coronary blood flow is induced by intracoronary artery injection of the blood obtained during, or 15 seconds after, the stimulation of the sympathetic nerve. This conclusion can be stated thus: the coronary venous blood samples, obtained while the coronary flow was increased following sympathetic stimulation, caused the marked augmentation of coronary blood flow. This finding is clearly demonstrated in Fig. 19, which illustrates the relationship between the coronary blood flow pattern and the increasing rate of coronary blood flow following the injection of each coronary sinus blood sample. In this figure the increase in coronary blood flow following sympathetic stimulation consists of two phases: the initial

increased response at the early time, during the stimulation, and the late response at the later time, after the stimulation. It seems that the coronary venous blood samples, obtained during the time corresponding to the increased responses, increase coronary blood flow remarkably.

The increase in coronary blood flow following the intracoronary injection of coronary blood samples is not associated with any remarkable changes in hemodynamics and modification of the heart; therefore, it may be suggested that some coronary vasodilatative substances are present. Although Eckstein and associates[28] stressed the vasodilatative effect of hemolysis caused by rapid injection, we did not see such a response.

Thus, we believe that our experiments demonstrated that some coronary vasodilatative substances were present in the coronary venous blood, and that they might play an important role in the sympathetic coronary vasodilatative action. Especially in the late increased response of coronary blood flow the hemodynamic changes are too slight to cause so marked an augmentation of coronary blood flow; therefore, these vasodilatative substances may be the most effective factor.

The exact nature of the coronary vasodilatative substances thus demonstrated is difficult to determine, and at present we cannot say what they are. But it seems to be significant that they increase the coronary blood flow without any hemodynamic changes, and that their effect appears immediately after the injection and persists only for 10 to 20 seconds. The coronary blood flow pattern induced is similar to that following the intracoronary injection of ATP, and differs greatly from that following the injection of norepinephrine (Fig. 20). It is also

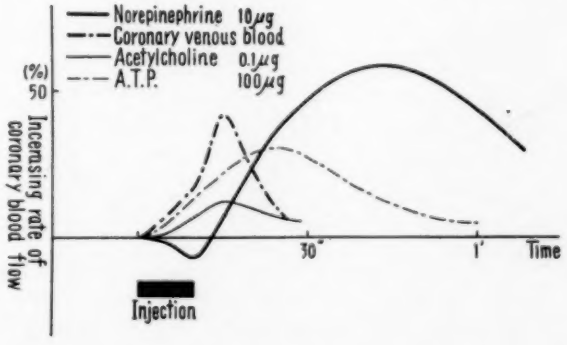

Fig. 20.—Increasing rate of coronary blood flow following the intracoronary artery injection of norepinephrine, coronary venous blood, acetylcholine, and ATP.

important to note that the effective blood samples were obtained during the time corresponding to the increase in vigor of cardiac contraction. On the basis of these findings it seems that the coronary vasodilatative substances thus demonstrated may be metabolites released following the sympathetic stimulation. At least they are not identical with norepinephrine itself. Moreover, the vasodilatation due to hypoxia following the intracoronary artery injection of the coronary venous blood may be ruled out, because the oxygen volumes contained in the

blood samples are not so different from each other (unpublished data); moreover, 0.85 per cent saline solution did not cause a marked increase in coronary blood flow.

On the other hand, the coronary vasodilatative effect of norepinephrine is far different from that of the other materials studied. As shown in our experiments, its effect appears slowly after the injection and persists for several minutes. The elevation of blood pressure and the increase in heart rate and vigor of contraction are always associated. It is an important fact, too, that sometimes the highest increase in the coronary blood flow is reached after heart rate and blood pressure have returned to the former level. Moreover, a large dose of norepinephrine decreased the coronary blood flow initially.

Thus, the coronary blood flow pattern following the intracoronary injection of norepinephrine is not similar to that following the injection of acetylcholine or ATP, but is very similar to that following the sympathetic stimulation. It seems that the coronary vasodilatative effect of norepinephrine is not essentially different from that of the sympathetic nerve.

The action of epinephrine on the coronary blood flow has been investigated extensively, and it is generally accepted that the action of norepinephrine on the coronary vessels is qualitatively the same as that of epinephrine.[23,29,30] In most dog and rabbit preparations, intracoronary artery injection of epinephrine or norepinephrine increases coronary blood flow. But in these instances there is also an associated elevation of blood pressure and an increase in cardiac metabolism, vigor of contraction, and heart rate, so that it is difficult to ascertain their direct action on the coronary vessels. Many workers found that following the injection of epinephrine, the coronary blood flow simultaneously increased with the elevation of blood pressure; but only Shipley and Kohlstedt[31] indicated that this response is preceded by a transient period of increase in coronary blood flow without change in blood pressure. They concluded that this result indicated a direct dilatative effect of epinephrine on the coronary vessels, but nobody has yet confirmed their finding. Lu and Melville[23] stated that the injection of norepinephrine or epinephrine into the coronary artery of the isolated rabbit heart decreased coronary blood flow initially and later increased it markedly; moreover, the augmentation of coronary blood flow always followed the evidences of irritation of the myocardium. Recently, Nakazawa[32] reported a similar observation, and these findings are very similar to ours. We suspect that the increase in coronary blood flow following the intracoronary injection of norepinephrine may result from its hemodynamic and metabolic effects. The direct action of norepinephrine on the coronary vessels may be rather vasoconstrictive, as is that of the sympathetic nerves, but we cannot stress this opinion at the present stage.

Dörner[33] suggested that the coronary vasodilatative action of epinephrine and norepinephrine may be due to the reflex effect, but at present we have no decisive data.

SUMMARY

1. A study was made of the coronary vasodilatative effects of coronary

venous blood samples obtained following the stimulation of the sympathetic and vagal nerves, and of norepinephrine, acetylcholine, and ATP.

2. In the coronary venous blood samples, obtained either during or 15 seconds after the stimulation of the sympathetic nerves, some vasodilatative substances were demonstrated. They may play one of the important roles in sympathetic coronary vasodilatation. The exact nature of the vasodilatative substances are unknown, but they may be the metabolites released following the sympathetic stimulation.

3. The coronary vasodilatative effect of norepinephrine differs in nature from that of acetylcholine, ATP, and effective coronary venous blood. It may result mainly from hemodynamic and metabolic action due to the modification of the heart. The action of norepinephrine on coronary vessels seems to be identical with that of the sympathetic nerves.

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Study of the Sequence of Ventricular Activation and the QRS Complex of the Pathologic Human Heart, Using Direct Epicardial Leads

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The sequence of the ventricular activation spread and the QRS complex morphologies in different points of the epicardial surface of the normal human heart have been reported in previous papers.[1-4] In one of them[1] our first results in pathologic hearts were published. Since then we have studied a greater number of cases, and by means of a larger pericardial opening we have been able to search for a greater number of points in the epicardium. The present paper is intended to report our new findings.

MATERIAL AND METHOD

Thirty-one patients, submitted to various types of pulmonary and cardiac surgery, were studied.

Eight cases were of chronic cor pulmonale. Two of them showed a classical pattern of right ventricular hypertrophy with a great degree of pulmonary hypertension (tall R wave in Lead V_1 and either RS or rS morphologies in left precordial leads). The other 6 showed the classical electrocardiographic pattern of emphysematous chronic cor pulmonale,[16,22] with or without right bundle branch block.

Eight cases were of mitral stenosis. Five of them showed a classical P mitrale and ÂQRS deviated to the right, and, sometimes, in Lead V_1 a QRS complex of small amplitude (not proportional to the ones obtained in the other precordial leads), of either rs, rsr′, rSr′, qr, or rS types. The other 3 cases showed Rs and qRs, respectively, in Lead V_1 and left precordial leads.

Two cases were of pure pulmonary stenosis, 5 cases of Fallot's tetralogy, and 1 case of Fallot's trilogy. All of them showed a classical right ventricular pattern with great hypertension.

Five cases exhibited left ventricular hypertrophy (1 with persistent ductus arteriosus without pulmonary hypertension, 2 with aortic aneurysms, 1 with essential hypertension, and 1 with double aortic lesion).

The last 2 cases showed biventricular hypertrophy (1 with atrioventricularis communis and 1 with persistent ductus arteriosus and pulmonary hypertension).

There were 15 males and 16 females. Twenty-six were white, 4 were Negroes, and 1 was Oriental. Their ages ranged from 3 to 36 years. The younger ones were operated on for Fallot's tetralogy and the older ones for pulmonary diseases.

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The technique, method, and instruments were the same as described previously.[1,4] Unfortunately, the epicardium was not explored on its whole surface, as would be desirable, because there were difficulties due to the surgical opening of the chest. Therefore, in some cases only the anterior surface of the right ventricle was explored, in others the anterior and lateral surface of the left ventricle, and in the remainder the anterior surface of the right ventricle and the anterior and lateral ones of the left ventricle. Occasionally, auricular points were taken.

RESULTS

I. *Morphology of the QRS Complex.*—

1. Figs. 1 to 4 show what is obtained in cases of chronic cor pulmonale, mitral stenosis, and pure or associated pulmonary stenosis with classical pattern of right ventricular hypertrophy. Fig. 5 shows a case of chronic cor pulmonale with right bundle branch block. In other cases of chronic cor pulmonale, mitral stenosis, and pulmonary stenosis, all showing a classical pattern of right ventricular hypertrophy, it was possible to obtain QRS complex of RS or qRs types in the pulmonary conus. In some cases the onset of the Q wave's inscription was synchronous in both leads, namely, the epicardial and the peripheral. In other cases it was later in the epicardial lead, thus suggesting an initial isoelectric phase for its explanation. In one of the cases of Fallot's tetralogy an exceptional rS pattern was recorded on the pulmonary conus.

2. In cases of chronic cor pulmonale with classical electrocardiographic pattern of emphysema, in cases of mitral stenosis without tall R wave in Lead V_1, and also in cases of left ventricular hypertrophy, the QRS morphologies obtained by means of the epicardial leads might have been indistinguishable from the normal. In one of the cases of left ventricular hypertrophy (Fig. 6) QS, QrS, and Q (r) S patterns were obtained in the upper part of the anterior portion of the left ventricle in an area larger than that in normal cases.

3. The cases of persistent ductus arteriosus and biventricular hypertrophy showed morphologies similar in their patterns and distributions to the ones obtained in cases with classical patterns of right ventricular hypertrophy.

4. The case of atrioventricularis communis showed QRS complexes with double R waves but without delayed S at the base of the right ventricle.

II. *QRS Complex Amplitude and Spread of Ventricular Activation.*—

Tables I, II, III, and IV (the first three corresponding, respectively, to Figs. 1, 3, and 6, and the fourth to the case with double aortic lesion) are quite illustrative, for from them one can see the fundamental data regarding the amplitude of the QRS complex in the different regions and, also, the sequence of activation spread on the epicardial surface.

TABLE I

	POINT	MORPHOLOGY	R (SEC.)	S (SEC.)	AMPLITUDE	R/S QUOTIENT	I.I.T. (SEC.)
Right Artium	1	QS		0.044	8.4		−0.014
	2	rSr′	0.012	0.044	0.3/9.8/0.9	0.30	−0.022
	3	rSr′?	0.016	0.040	0.4/7.4/?	0.54	−0.018
	4	rSr′	0.016	0.044	0.3/7.6/0.5	0.039	−0.018
Right Ventricle	5	rS	0.032	0.050	7.8/13.7/7.8	0.57	−0.020
	6	rS	0.032	0.060	3.2/7.7	0.40	−0.018
	7	rRs	(0.020) 0.056	0.054	8.0/3.1		−0.018
	8	rRs	(0.022) 0.058	0.070	11.3/1.5		−0.016
	9	rRS	(0.020) 0.046	0.062	7.4/6.1	1.20	−0.024
A.S.P.	10	rS	0.032	0.046	12.2/20.6	0.50	−0.014

I.I.T. = Initial inscription time. A.S.P. = Anterior septal projection.

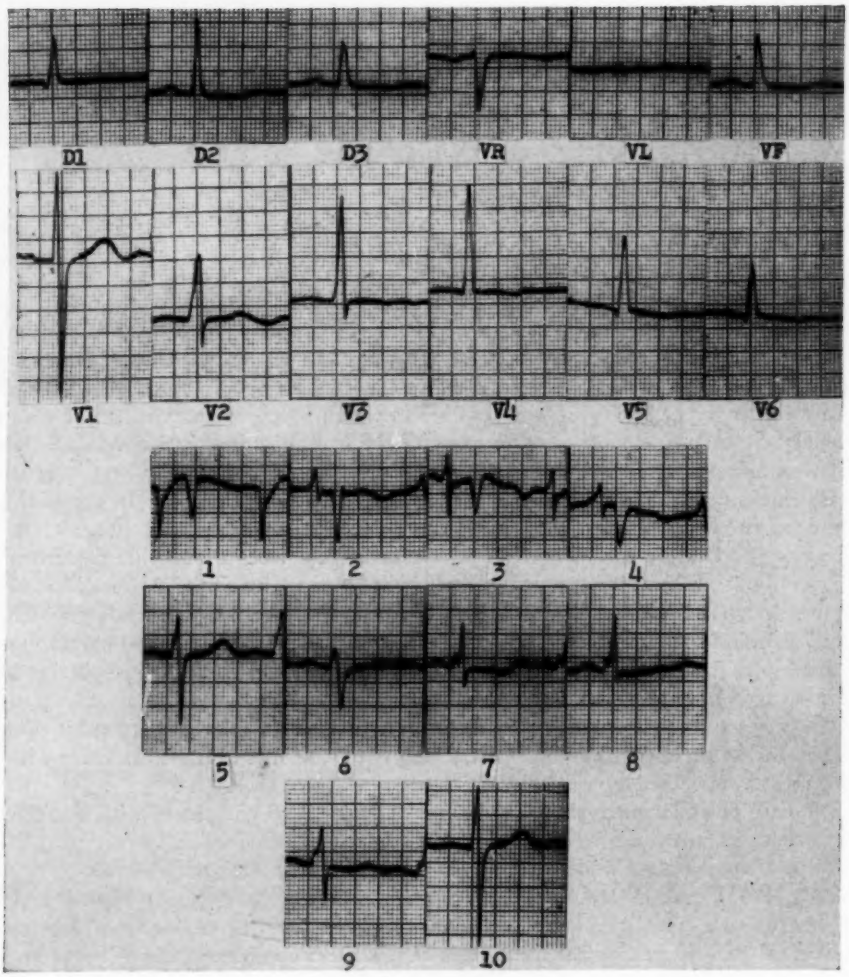
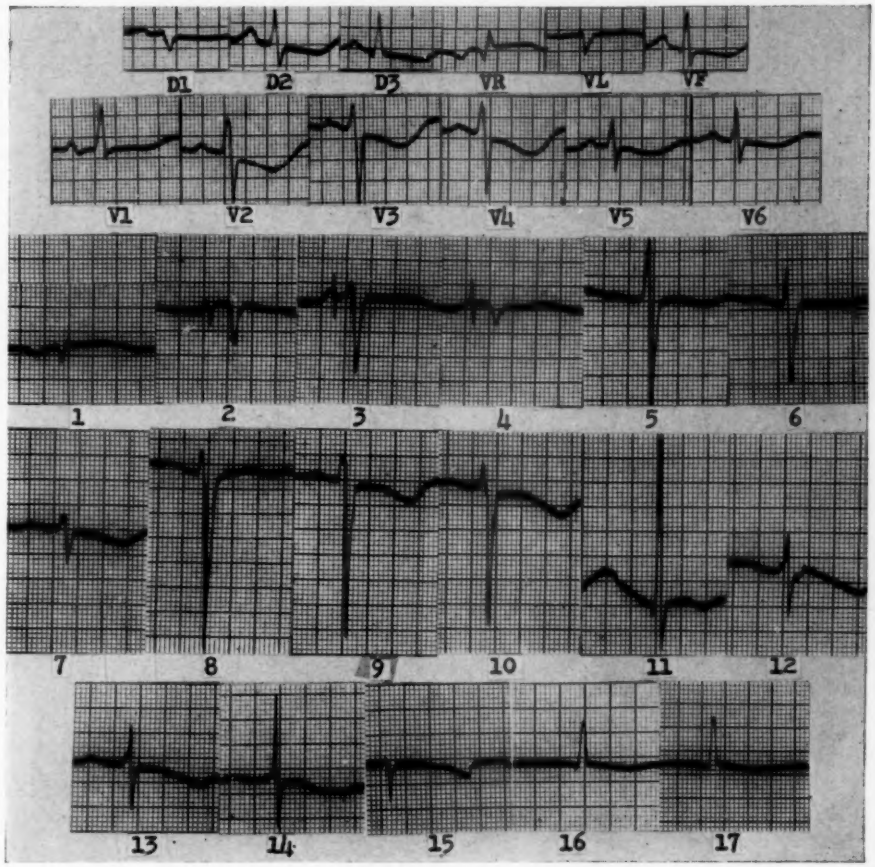
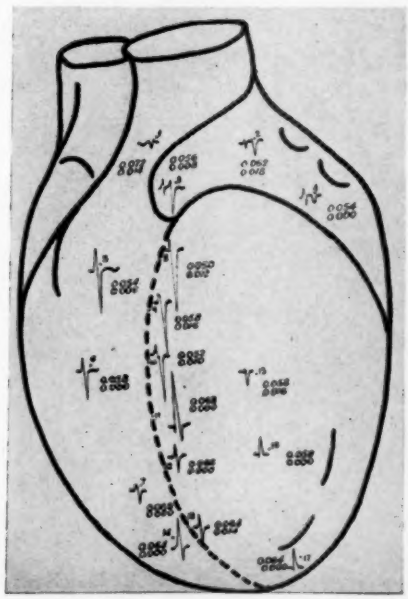


Fig. 1.—G. R., a 25-year-old white man with chronic cor pulmonale.

In this and all subsequent figures, *A* shows standard leads, unipolar limb leads, precordial leads, and direct epicardial leads, and *B* shows localization of the recorded epicardial points. In *B* the upper number corresponds to the time of arrival of the stimulus on the epicardial surface, while the lower number indicates the interval between the onset of the first ventricular deflection in direct leads and that in indirect leads.



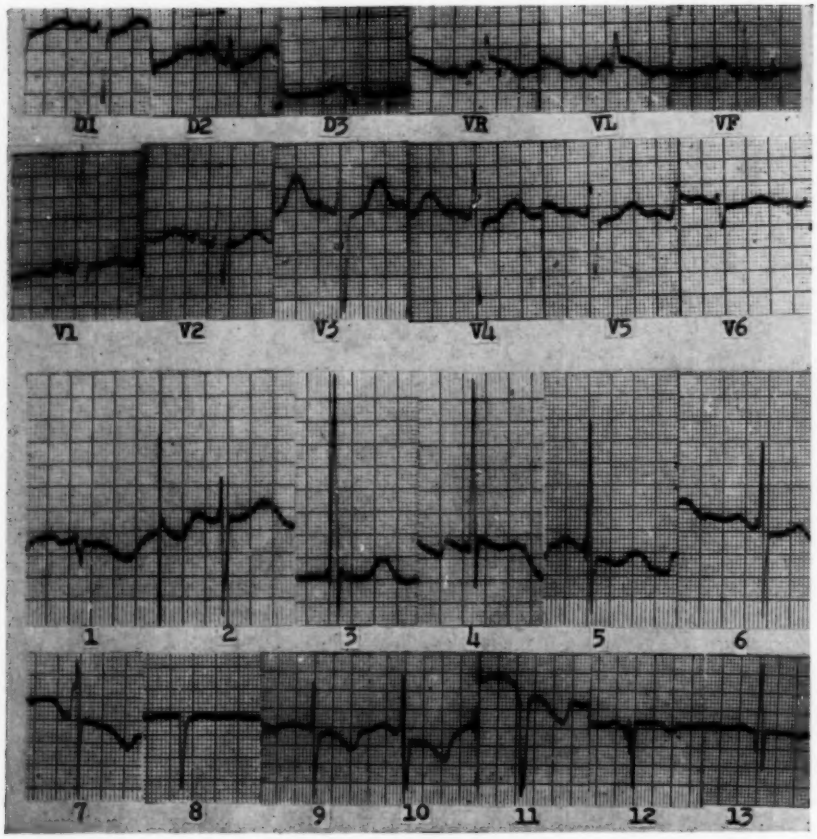
A.



B.

Fig. 2.—D. M., a 33-year-old white woman with pure mitral stenosis.

A.



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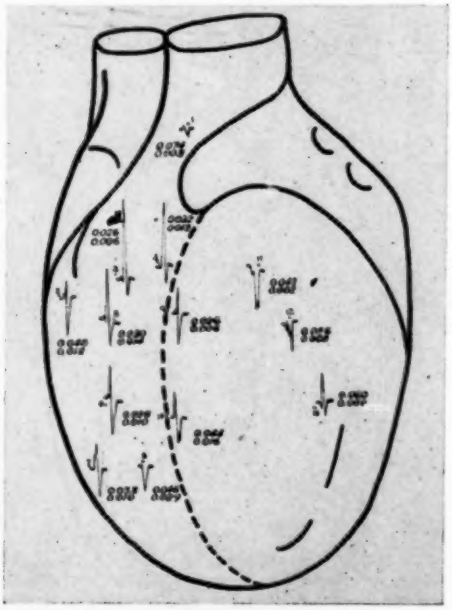
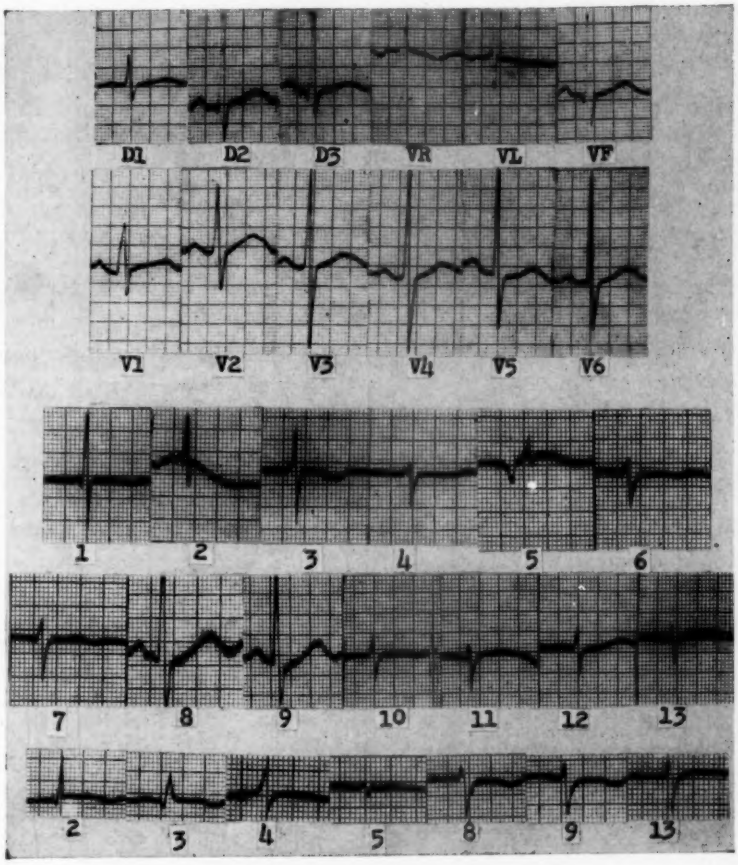


Fig. 3.—I.R.A., a 5-year-old white boy with Fallot's tetralogy.



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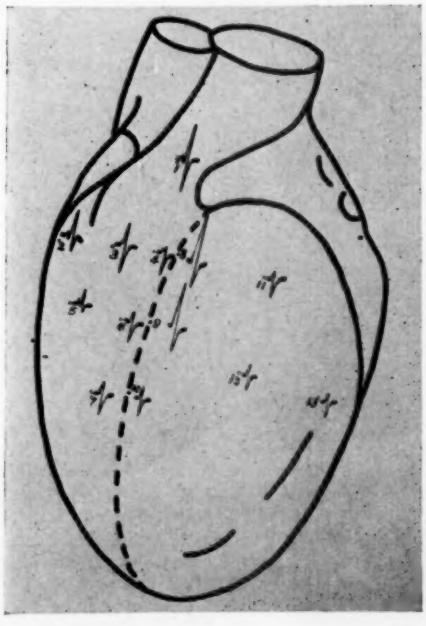


B.

Fig. 4.—N. M., a 9-year-old white girl with pure pulmonary stenosis.

DISCUSSION

Our data show that the trabecular zone in right ventricular hypertrophy is still the portion to be activated earliest; however, activation is later than in the normal heart. Therefore, the time lag between the points to be first activated in the right and the left ventricles is shortened. The representative vector of the mean activation spread is directed to the right and forward, sometimes upward, just as has been foreseen by means of the vectorcardiogram.[8,13,14]

In cases of extreme hypertrophy the mean activation process is still from the apex to the base, but the time lags between the activation of different points of the right ventricle are greater and not proportional to those observed in normal cases and moderate hypertrophies. In conclusion, there is in these cases not only

TABLE II

	POINT	MORPHOLOGY	Q (SEC.)	R (SEC.)	S (SEC.)	R′ (SEC.)	AMPLITUDE	R/S QUOTIENT	I.I.T. (SEC.)
P.A.	1	r(s) Sr′		0.026	(0.036) 0.056	0.074	1.4/4.5	0.31	0.008
Right Ventricle	2	(r)rS		(0.022) 0.036	0.046		9.0/20.5	0.07	0.012
	3	rsRs		0.016	0.026		1.5/1.0/44.6/10.0	1.50	0.006
	4	rsRs		0.022	0.032		1.3/0.6/37.3/ 9.1	2.10	0.012
	5	rsRs		0.020	0.030		1.2/2.3/27.2/10.7	0.52	0.014
	6	rsRs		0.020	0.026		1.7/0.1/17.2/18.2	1.70	0.010
	7	(r)RS		(0.022) 0.044	0.058		12.2/16.1	0.75	0.010
A.S.P.	8	rS		0.032	0.046		0.3/15	0.02	0.029
	9	rsRS		0.018	0.026		0.9/1.2	0.75	0.006
	10	RS(s)		0.030	0.044 (0.058)		14.9/14.6	1.08	0.016
L.V.	11	r(r)S		0.008 (0.026)	0.042		0.1/29.6	0.003	0.002
	12	qr(sr′)S	0.020	0.032	(0.042–0.048) 0.056		3.0/ 5.8/17.1	0.17	0.008
	13	qRs	0.022	0.046	0.060		5.2/17.9/10.0	1.70	0.000

P.A. = Pulmonary artery. L.V. = Left ventricle. A.S.P. and I.I.T. as in Table I.

TABLE III

	POINT	MORPHOLOGY	Q (SEC.)	R (SEC.)	S (SEC.)	AMPLITUDE	R/S QUOTIENT	I.I.T. (SEC.)
P.A.	1	rS		0.030	0.054	2.7/9.3	0.3	0.000
	2	RS		0.026	0.048	5.3/6.5	0.8	−0.000
Left Ventricle	3	qRS	0.008	0.022	0.040	1.8/ 8.0/ 7.0	1.00	−0.008
	4	QrS	0.014	0.030	0.042	5.4/ 2.3/14.5	0.16	−0.012
	5	QrS	0.016	0.034	0.040	7.2/ 1.0/21.2	0.04	−0.020
	6	QRS	0.016	0.038	0.048	6.0/11.3/16.5	0.60	−0.020
	7	QRS	0.032	0.042	0.048	5.7/11.1/16.5	0.60	0.010
	8	qR	0.008	0.040	0.070	0.2/14.9		0.010
	9	qRs	0.009	0.042	0.056	0.7/23.7/ 5.2	4.50	0.018
	10	qRs	0.009	0.032	0.058	3.2/31.5/ 5.2	6.20	0.024

a delay in the onset of the activation spread on the epicardial surface of the right ventricle, but also a change in the pattern of activation spread of this ventricle.

In certain cases of chronic cor pulmonale and pulmonary stenosis the activation is much delayed in the pulmonary conus and the adjoining portions of the intermediate zone of the right ventricle. In such cases, RS, Rs, rRs, rsR′S′, rsR′s′, and qRs patterns were obtained in those zones. The localized hypertrophy of the outflow tract of the right ventricle, which has already been found in such cases,[1,5,19] might explain the greater delay in the activation spread of the pulmonary conus. Furthermore, for the proper interpretation of the delayed R wave in this region one could admit a localized block in the outflow tract, as suggested by Barbato[1] and Walker and associates.[21] That this is very likely is shown by the evident dissociation between the initial vectors (septal and paraseptal) and the delayed ones, which are responsible, respectively, for the initial and the delayed R waves. One cannot disregard the hypothesis of both factors, namely, increase in the ventricular thickness and localized block, acting together.

Right bundle branch block is not the explanation for the above-mentioned morphologies, because there is an rS pattern without a broader S wave in scattered points in the right ventricle, especially in the paraseptal zone, similar to that which occurs in the normal heart. In the left ventricle the QRS complexes also maintain the normal pattern.

TABLE IV

	POINT	MORPHOLOGY	R (SEC.)	S (SEC.)	R′ (SEC.)	S′ (SEC.)	AMPLITUDE	R/S QUOTIENT	I.I.T. (SEC.)
P.A.	1	rSr′	0.038	0.052	0.068		2.0/4.0/2.6	0.50	—0.018
	2	RSR′S′	0.052	0.052	0.066	0.082	4.6/6.0/4.3/5.6	0.70	—0.010
Right Ventricle	3	rS	0.032	0.052			4.3/18.0	0.20	—0.014
	4	rS	0.024	0.058			2.4/17.8	0.10	—0.002
	5	rS	0.038	0.054			4.0/15.2	0.26	—0.008
			Q	R	S				
	6	qRS	0.030	0.054	0.086		1.1/12.8/ 9.5	0.65	—0.024
			R	S	R′				
	7	rSr′	0.026	0.038	0.072		3.0/20.3/ 2.4	8.40	—0.000
			Q	R	S				
	8	qRS	0.020	0.052	0.068		1.1/15.7/12.6	1.20	—0.006
A.S.P.	9	qRS	0.022	0.050	0.060		1.5/18.6/22.0	0.80	—0.014
	10	qRS	0.026	0.048	0.056		2.0/20.2/17.9	1.10	0.000
Left Ventricle	11	qRS	0.016	0.040	0.052		0.2/ 10.4/18.3	0.50	—0.008
			Q	R	S				
	12	QRS	0.030	0.052	0.076		3.9/ 5.6/16.4	0.30	—0.010
	13	qRs	0.028	0.062	0.074		0.8/ 5.3/ 0.5	10.60	—0.005
	14	QRs	0.032	0.082	0.096		8.0/ 34.8/ 2.7	12.80	—0.004
	15	qRs	0.032	0.068	?		32.5/292.5/?		—0.014
	16	qRs	0.028	0.052	0.064		15.0/120.0/37.5	32.40	—0.012
	17	qRs	0.034	0.068	0.084		32.5/405.0/ 5.0	81.00	—0.016
	18	qRs	0.038	0.082	?		35.0/262.5/?		—0.008

It is worth mentioning that in spite of a delayed activation spread in these regions the presence of a final S wave (except in the case of atrioventricularis communis) shows that they are not the last to be activated.

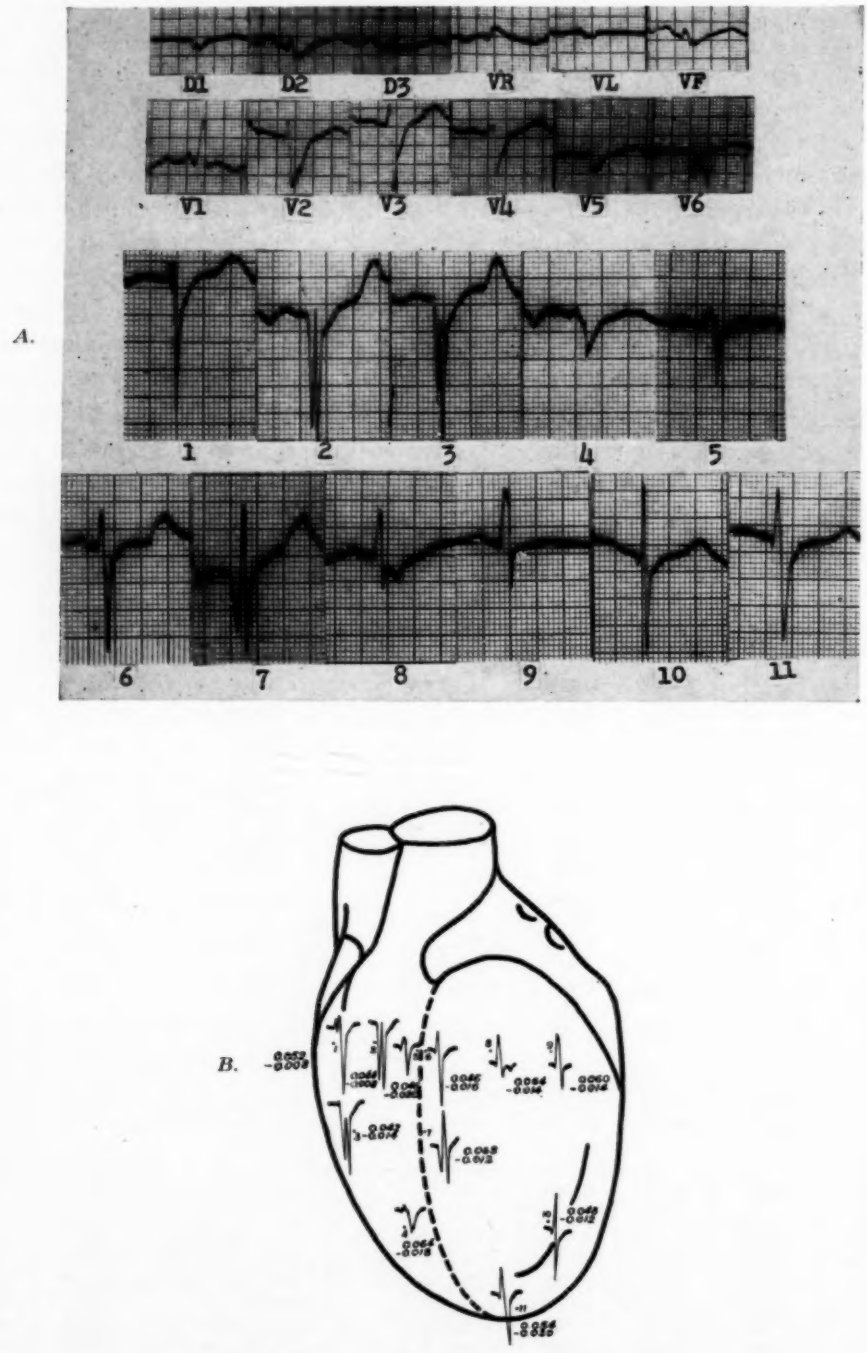
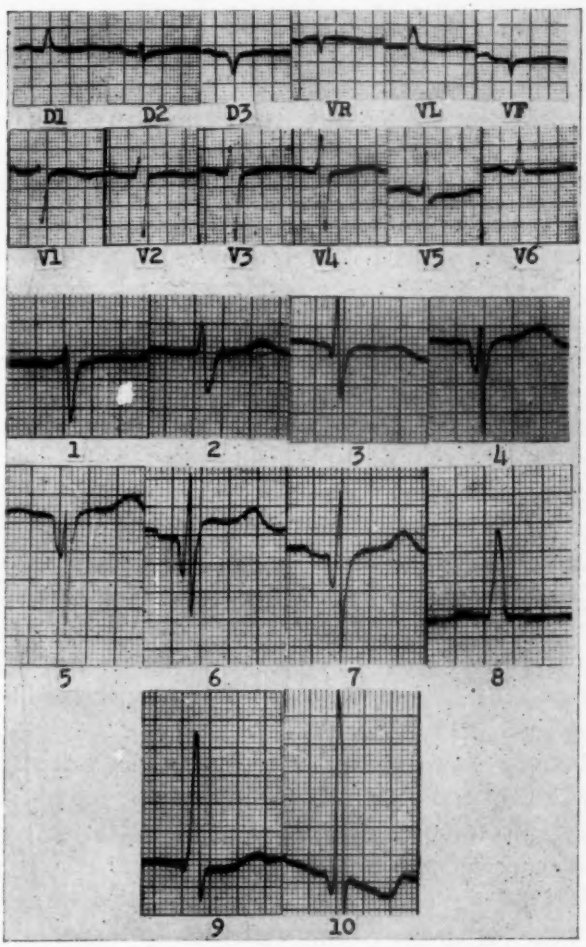
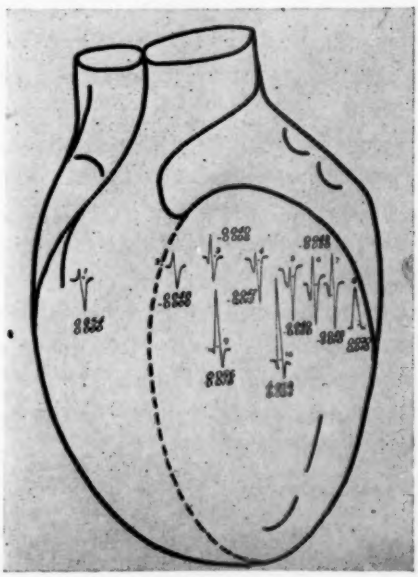


Fig. 5.—J.J.R., a 24-year-old white man with chronic cor pulmonale.



A.



B.

Fig. 6.—R. M., a 58-year-old white man with essential hypertension, who was operated on for bronchogenic carcinoma.

In left ventricular hypertrophy there is, basically, a delay in the activation spread at the base of the left ventricle in its lateral surface, near the posterior surface, without changing the activation's normal sequence. This explains why in this hypertrophy the last cardiac vectors are deviated more to the back and to the left.[10] Since the pattern of activation spread in left ventricular hypertrophy is but an exaggeration of the normal, one readily understands the hypothesis[20] that the left ventricle dominates the activation spread of the normal heart and, therefore, fundamentally determines the normal vectorcardiogram.

The activation in the septum spreads from the left to the right in left ventricular hypertrophy, and also in the majority of cases of right ventricular hypertrophy. It is rarely inverted, as it was in one of our cases of pulmonary stenosis. In almost every case the QRS complex shows an initial negative deflection over the left ventricle and an initial positive deflection over the right ventricle. This is very important from the practical point of view for there is, to some extent, a relationship between the thoracic and epicardial surfaces.[6,7,11,17] In some cases of right ventricular hypertrophy the presence of a Q wave in the right ventricular surface is due to the inversion in the direction of the septal activation, as maintained by several authors.[9,12,18] In other cases the Q wave's onset on the right ventricular surface is much later than its beginning in the peripheral simultaneous leads. Therefore, one has to admit either an isoelectric period (equilibrium of opposite forces) or an initial R wave which does not inscribe because of low sensitivity of the usual instruments.[14,18]

It should not be forgotten that on the right ventricular surface the complexes with initial Q wave are of the qRS and qRs patterns. No qR patterns are registered as in the auricles and pulmonary artery. In the latter, one can also obtain morphologies such as an rSr′ pattern.

The so-called transitional patterns (RS and qRS) are found in the same regions both in normal hearts and in those with left ventricular hypertrophy, namely, in the lower halves of the left portions of the anterior projection of the septum and of the left paraseptal zone. In right ventricular hypertrophy such patterns might be found in the intermediate zone of the right ventricle and, sometimes, in the pulmonary conus.

In cases with right bundle branch block, polyphasic complexes—W, rSr′s′, rSr′S′—are obtained over all the anterior surface of the right ventricle. In the apex of this ventricle one obtains rS morphologies with notches in the R and broad S waves. Over the left ventricle one obtains QRS complexes of qrS and qRS pattern, with broader and thicker S waves.

Ordinarily, the increase in the amplitude of the QRS complex in both hypertrophies is slightly significant in relation to the cases of pulmonary stenosis; in cases of left ventricular hypertrophy (Tables III and IV) its increase in the lateral surface is so great that one has to reduce the normal time standardization twenty fold instead of the usual fourfold.

SUMMARY AND CONCLUSIONS

In 31 patients with either right or left ventricular hypertrophy, submitted to pulmonary or cardiac surgery, direct epicardial leads were recorded for the

sake of studying the spread of ventricular activation and QRS morphologies in different points on the anterior and lateral ventricular surfaces.

In cases of slight right ventricular hypertrophy there is only a delay in the onset of activation in all points of the right ventricular surface. Therefore, the time lag between the activation of the first points in both ventricles is shortened.

On the other hand, however, the pattern of activation spread is very much altered in cases of severe right ventricular hypertrophy, not only in the right ventricle but in the heart as a whole. The principal change is a delay of the activation in the outflow tract of the right ventricle. In this region, patterns such as rsR′s′, rsR′S′, rRs, and qRs may be obtained. The genesis of the latter morphologies is discussed.

In left ventricular hypertrophy there is a delay in the activation over all points of the left ventricular surface, especially in the most basal and lateral points of its lateral surface. However, the sequence of activation and the morphology of the QRS complex is not significantly altered.

The electrocardiographic transition zone in left ventricular hypertrophy occupies the same points as in normal hearts. In right ventricular hypertrophy it extends to the right ventricle's intermediate zone and, occasionally, to the pulmonary conus.

In one case of pure pulmonary stenosis an inversion in the spread of septal activation was demonstrated.

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The Electrocardiogram in Cor Pulmonale Secondary To Pulmonary Emphysema: A Study of 18 Cases Proved by Autopsy

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For several reasons it is of interest to report the observations on the electrocardiograms in a group of 18 patients who died with congestive failure due to cor pulmonale secondary to pulmonary emphysema: The incidence of pulmonary emphysema appears to be increasing.[1] Recognition of a major complication becomes of greater importance. Disagreement appears to exist concerning the value of the cardiogram in chronic cor pulmonale. Some authors hold that the ECG may be the first clue to the diagnosis of right ventricular hypertrophy,[2] presenting abnormalities early in the disease and helping to delineate the type of abnormality found in the lesser circulation.[3] Others maintain that ECG abnormalities in right heart disease usually occur late or sometimes not at all.[4] Separate consideration is needed for the entity of chronic cor pulmonale secondary to pulmonary emphysema as distinguished from right ventricular hypertrophy associated with other disease entities, such as congenital heart disease, rheumatic heart disease, and pulmonary hypertension due primarily to lesions of the pulmonary vascular tree. The need to consider emphysema heart disease separately has been mentioned by other authors[4,5] and will be discussed later. This has not been done in many excellent studies of right ventricular hypertrophy which have reported cases with right ventricular hypertrophy of diverse etiology. The number of cases reported with chronic cor pulmonale due to emphysema was often small, the majority of patients having either congenital or rheumatic lesions.

Autopsy studies on emphysema heart disease are relatively infrequent. In some there is only a brief description of the ECG data, or the studies were made before the 12-lead ECG was in common use.[6] Others fail to give complete information about the type of lung disease present, so that one does not know whether emphysema was the predominant lung lesions.[7,4a]

METHOD OF THE PRESENT STUDY

Eighteen consecutive patients with chronic cor pulmonale secondary to pulmonary emphysema were studied. In each the diagnosis was proved by autopsy. All patients had been seen

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by the author during the terminal part of their illness and showed evidence of advanced pulmonary insufficiency as well as congestive heart failure. All were considered by the pathologist to have died as the result of chronic cor pulmonale and pulmonary emphysema.

The autopsy criteria for cor pulmonale and right ventricular hypertrophy used in this study were as follows: (1) thickness of the right ventricular wall measured 5 mm. or more[4a,6,6a]; (2) heart weight exceeded the mean standard deviation for body weight[4a]; (3) absence of clinical or autopsy evidence of other types of heart disease[4a,6,6a]; or, if additional lesions were present, the pathologic changes from emphysema and cor pulmonale predominated. In this regard, there were only 2 patients who had evidence of heart disease in addition to cor pulmonale. Case 2 had aortic stenosis and Case 11 had patchy fibrosis in the myocardium. In each instance the thickness of the right ventricle showed a relatively greater increase as compared with the thickness of the left ventricle.[4]

The data recorded for each patient were as follows: A 12-lead ECG (3 standard leads, 3 unipolar leads, and 6 precordial leads taken in the commonly recommended positions) was taken within 1 month of death. In 4 patients comparison of the last tracing with previous ones was possible and helped to delineate the development of the electrocardiographic picture of cor pulmonale. Certain clinical data pertinent to the problems of chronic cor pulmonale and pulmonary emphysema were tabulated. These included age, history of chronic cough, previous pulmonary infection (such as pneumonia), presence of allergy in the form of bronchial asthma, occupation (with special regard for the dusty trades), and smoking habits. Laboratory data concerned with secondary polycythemia and respiratory acidosis were tabulated. Autopsy findings pertaining to the heart and lungs were outlined, such as heart weight, average thickness of the individual ventricular walls, evidence of other associated heart disease (such as valvular or coronary artery lesions), the presence of emphysema and lesions of the tracheobronchial tree (such as chronic bronchitis and bronchiectasis).

The following pathologic criteria for pulmonary emphysema were employed: (1) Grossly, the lungs were diffusely overdistended and bulging. On opening the chest they did not collapse. Subpleural blebs were commonly noted. The bronchi contained increased mucoid secretion, and the mucosa appeared injected. (2) Microscopically, all lobes showed dilated alveolar spaces and thinned alveolar walls which were often ruptured with coalescing of several alveolar spaces. (3) Chronic bronchitis was considered to exist if, microscopically, there was an increase in the number of bronchial mucous glands, hyperemia of the mucosa, and infiltration of the wall with chronic mononuclear inflammatory cells.

ANALYSIS OF THE ELECTROCARDIOGRAPHIC DATA

The findings in the ECG considered to be helpful in the diagnosis of cor pulmonale are evidence of P-pulmonale (usually defined as a tall, peaked P wave in Leads II, III, and aV_F measuring greater than 2.5 mm. in height) and evidence of right ventricular hypertrophy. Lack of agreement regarding criteria warranting a diagnosis of right ventricular hypertrophy poses a problem.

To some extent each report on the subject is accompanied by a new set of criteria held by the author to be superior to others for one reason or another. To obviate this problem, several sets of criteria for right ventricular hypertrophy were used in the analysis of the tracings. The standards used in this study were those of Sokolow and Lyon,[8] Milnor,[9] Scott,[10] and Grishman.[11] Others could have been chosen but these seemed representative. They are listed in Table I. In addition, the mean spatial vector was determined for each ECG according to the method of Grant.[12]

While criteria for the diagnosis of right ventricular hypertrophy differ to some extent, all depend, nevertheless, on two basic changes in the electrical forces in the ECG. One basic change is the orientation of the major electromotive forces toward the right rather than to the left. In the standard and unipolar frontal plane leads this is represented by the presence of "right axis deviation," and often a prominent R wave in Lead aV_R. In the unipolar chest leads the major rightward direction of the electromotive forces results in a failure of the evolution of the QRS to a tall R or qR over the left side, with a relatively prominent S wave remaining in these leads.

A second basic change in the ECG common to most criteria for right ventricular hypertrophy is orientation of the major electromotive forces in an anterior as well as rightward direction. This results in the development of a prominent R wave in the right precordial leads and/or special right chest leads, such as V_{3R}. These changes can be depicted by the three-dimensional concept of the mean spatial vector which to some extent simplifies diagrammatically the details included in the various criteria.

TABLE I. TABULATION OF SETS OF CRITERIA FOR RIGHT VENTRICULAR HYPERTROPHY

1. Sokolow and Lyon (American Heart Journal 38:273, 1949)
   One or more of the following criteria indicates RVH
   - R in V_1 is 7 mm. or more
   - S in V_1 is less than 2 mm.
   - S in V_5 or V_6 is 7 mm. or more
   - Sum of R in V_1 plus S in V_5 and V_6 equals 10.5 mm. or more
   - R in V_5 or V_6 is less than 5 mm.
   - Ratio of R/S is 1.0 or less in V_5 or V_6
   - Ratio of $\frac{\text{R/S in } V_5}{\text{R/S in } V_1}$ is 0.4 or less
   - Under the age of 5 years the ratio of R/S in V_1 exceeds 4
   - Over the age of 5 years the ratio of R/S in V_1 exceeds 1
   - Intrinsicoid deflection measures 0.04 to 0.07 in V_1 or V_2
   - Marked right axis deviation of greater than +110 degrees
   - Depression of the S–T segment and inversion of the T wave in V_1 when the R wave exceeds 5 mm.
   - R in aV_R is 5 mm. or more

   (Cases of right bundle branch block were excluded from the study)
2. Grishman, et al. (American Heart Journal 50:591, 1955)
   In the absence of myocardial infarction or the pattern of "incomplete right bundle branch block," the figures of Kossmann for normal voltage limits are used (Kossmann: Circulation 8:920, 1953)
3. Milnor (Circulation 16:348, 1957)
   QRS less than 0.12 second in duration—mean frontal plane axis of QRS between +110 and +180 degrees; or − 91 and −180 degrees
   R/S or R′/S ratio of greater than 1 in V_1 with the R wave greater than 0.5 mv.
4. Scott, et al. (Circulation 11:927, 1955)
   - qR complex in V_{3R} or V_1
   - R in V_1 of 7 mm. or greater
   - Ratio of R/S in V_1 greater than 1
   - If incomplete right bundle branch block, the R′ is greater than 10 mm. in V_1 or V_{3R}
   - If complete right bundle branch block, the R′ is greater than 15 mm. in V_1 or V_{3R}
   - Intrinsicoid deflection of 0.35 to 0.05 second in V_1

RESULTS

Electrocardiographic Findings in 18 Autopsied Cases of Cor Pulmonale Secondary to Pulmonary Emphysema.—

1. *Axis deviation on the frontal plane:* Normal axis has been defined as zero to +90 degrees, right axis from +90 to +180 degrees, and left axis from 0 to −180 degrees.[13] Among the 18 patients, there were 5 with normal axis, 10 with right axis, and 3 with left axis deviation.

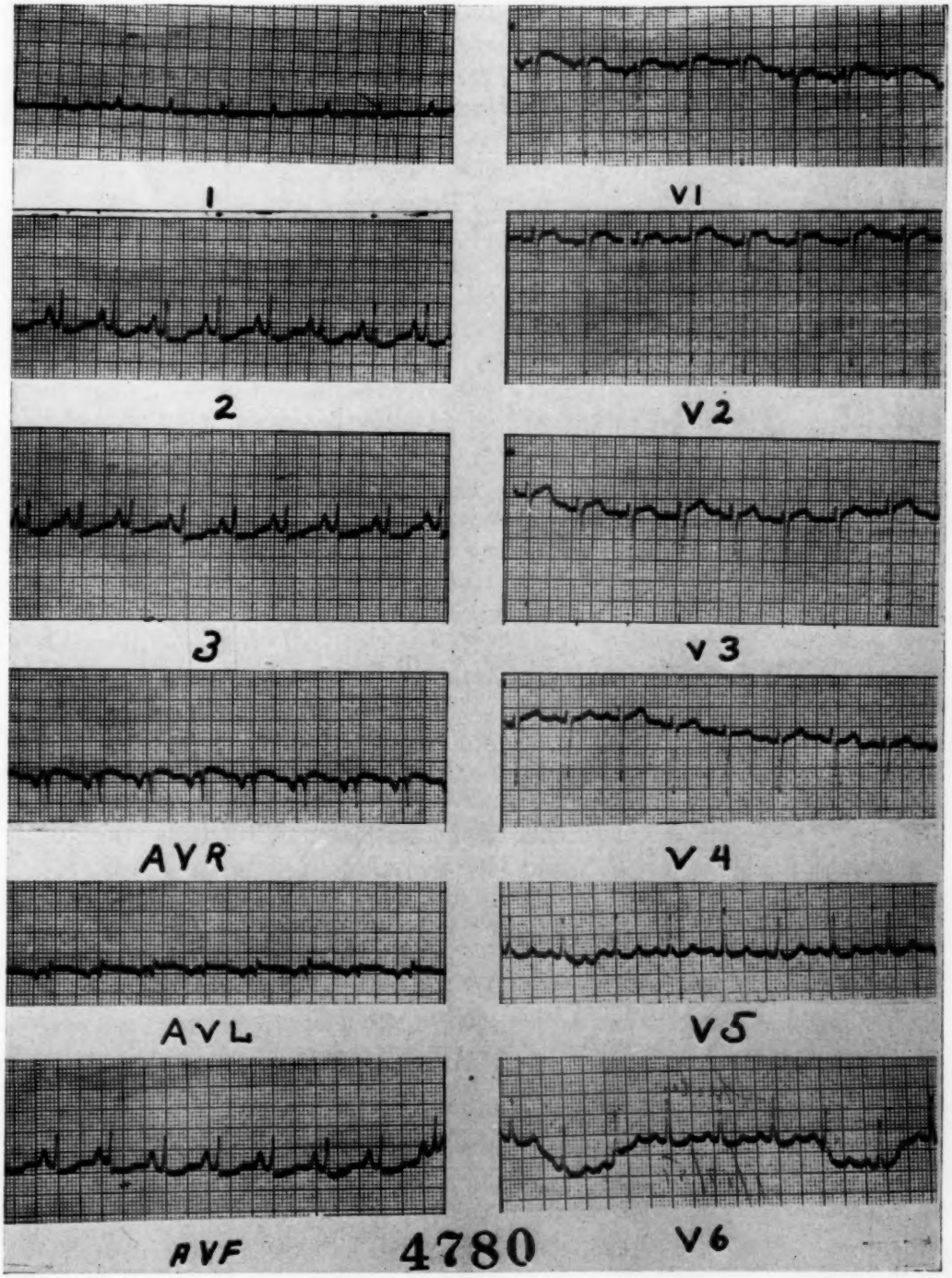

Fig. 1.—Case 11. Chronic cor pulmonale. The ECG illustrates the fact that P-pulmonale may occur without QRS changes which indicate right ventricular hypertrophy, and thus may be the only clue in the tracing to the presence of chronic cor pulmonale.

TABLE II. COR PULMONALE SECONDARY TO EMPHYSEMA

CASE	AUTOPSY DATA				ECG CRITERIA OF RIGHT VENTRICULAR HYPERTROPHY				
	AGE	HEART WEIGHT (GRAMS)	R.V. (MM.)	L.V. (MM.)	SOKOLOW	MILNOR	SCOTT	GRISHMAN	P-PULMONALE
1.	46	750	13	17	+	+	+	+	0
2.	62	725	7	14	+	+	+	+	0
3.	64	600	5	11	+	+	+	+	+
4.	58	550	9	13	+	+	0	0	0
5.	76	550	10	12	+	+	+	+	+
6.	53	550	5	12	+	+	0	0	0
7.	59	500	7	10	+	+	+	+	0
8.	58	500	12	15	+	+	+	+	+
9.	56	490	9	15	+	+	+	+	0
10.	61	450	9	12	+	+	0	0	0
11.	57	450	9	15	0	0	0	0	+
12.	59	425	5	10	+	+	0	0	0
13.	59	400	5	10	0	0	0	0	0
14.	52	400	8	14	0	0	0	0	0
15.	56	375	5	12	+	+	0	0	0
16.	59	375	6	11	0	0	0	0	0
17.	61	375	5	10	+	+	0	0	0
18.	60	375	8	14	0	0	0	0	0
Percentage of Patients					13/18 (72%)	13/18 (72%)	7/18 (38%)	7/18 (38%)	4/18 (22%)

TABLE II—CONT'D

CASE	OCCUPATION	CLINICAL DATA			LABORATORY DATA				
		CHRONIC COUGH	HISTORY OF PNEUMONIA	CIGARETTE SMOKING	BLOOD PRESSURE (MM. HG)	HEMOGLOBIN	HEMATOCRIT	CO_2*	CL*
1.	Jewelry	Yes	3 times in past 2 yr.	3 pk./day	130/80	20	72	34	96
2.	Plastic	Yes	2 times at age 13 yr.	2 pk./day	90/70	19.5	62	—	—
3.	Boat Builder	Yes	No	2 pk./day	140/80	14	48	36	87
4.	Textile	Yes	No	1 pk./day	130/80	18	57	31	87
5.	Foundry	Yes	Age 68 yr.	1 pk./day	110/64	——	—	—	—
6.	Cook	Yes	No	1½ pk./day	120/80	15	—	34	96
7.	Laundry	Yes	Age 55 yr.	1 pk./day	140/90	16.5	52	34	87
8.	Tinsmith	Yes	Age 10 yr.	1 pk./day	110/68	13.5	44	44	82
9.	Machinist	Yes	No	2 pk./day	116/70	16.5	55	39	91
10.	Gardener	Yes	No	1 pk./day	118/70	13.5	—	—	—
11.	Painter	Yes	No	2 pk./day	120/75	17.5	57	—	—
12.	Fireman	Yes	Age 54 yr.	1 pk./day	120/70	19	65	40	86
13.	Clerk	Yes	No	2 pk./day	130/70	13	45	30	96
14.	Clerk	Yes	No	2 pk./day	120/70	12	—	39	89
15.	Carpenter	Yes	No	1 pk./day	110/70	17	57	27	91
16.	Laundry	Yes	No	1 pk./day	130/80	14	—	30	91
17.	Machinist	Yes	No	2 pk./day	100/70	17	59	36	90
18.	Foreman	Yes	No	1 pk./day	116/70	13	—	31	94

*Milliequivalent per liter.

It should be noted that a rightward direction of major electromotive force could produce an axis deviation which would lie not only between +90 and +180 degrees (which would be considered right axis deviation) but also between −90 to −180 degrees (which by definition would be considered left axis deviation). This probably explains why right axis deviation in the frontal plane is not considered by some to be a reliable or consistent finding in cor pulmonale. However, if one considers that rightward direction of the major electromotive force is to be measured, then a direction of forces greater than +90 degrees or −90 degrees is the important feature to be considered. If one uses this concept of rightward direction of the major electromotive force in the frontal plane, then one finds that there were only 5 of the 18 patients without rightward direction of the mean frontal vector force. None of these 5 showed any other QRS criteria of cor pulmonale electrocardiographically. In the other 13 who had rightward direction of electromotive force there was also present other criteria of right ventricular hypertrophy.

2. *Occurrence of P-pulmonale:* As noted, P-pulmonale was considered to be present if there were tall, peaked P waves measuring over 2.5 mm. in height in Leads II, III, or aV_F. Such P waves were found in 4 (22 per cent) of the 18 patients, approximately the incidence found by Walker, Helm and Scott.[4a] It is worthy of note that in one of our patients (Case 11; Fig. 1) the presence of P-pulmonale was the only ECG abnormality consistent with cor pulmonale (the QRS configuration not fulfilling the criteria for right ventricular hypertrophy). We have observed this phenomenon occasionally in other patients; they were considered to have chronic cor pulmonale on clinical grounds, but were not included in this series because they did not come to autopsy. Therefore, the occurrence of P-pulmonale in chronic cor pulmonale due to emphysema is not frequent but may be a valuable clue to the diagnosis when noted.

3. *Occurrence of ECG evidence of right ventricular hypertrophy:* The degree of accuracy with which one could detect right ventricular hypertrophy by the four sets of criteria varied from 38 to 72 per cent. Interestingly, using the criteria of Scott and of Grishman in our 18 cases revealed evidence of right ventricular hypertrophy in the same cases (both detected right ventricular hypertrophy in 38 per cent of the 18 cases). Similarly, the criteria of Sokolow and Lyon and of Milnor detected right ventricular hypertrophy in the same cases, as well as in 72 per cent of the 18 cases. Correlation of the autopsy data with the various standards for right ventricular hypertrophy reveals a trend in the data which helps to explain these findings. This is outlined in Table II in which the patients are listed in order of decreasing heart weights. Those with hearts weighing over 500 grams generally satisfied all four sets of criteria for right ventricular hypertrophy. However, those with hearts weighing under 500 grams were detected only by the criteria for right ventricular hypertrophy established by Sokolow and Lyon and by Milnor (5 of the 10 with hearts under 500 grams did not satisfy any of the criteria for right ventricular hypertrophy). It seems clear that criteria which depend predominantly on orientation of the major electrical forces anteriorly do not detect right ventricular hypertrophy until it has become far advanced and terminal in chronic cor pulmonale. Thus,

those hearts with the greatest weight and thickness of the right ventricular wall tended to have an anterior as well as rightward direction of major electrical force, and were detected by those criteria for right ventricular hypertrophy which depended primarily on anteriorly directed forces. However, criteria for right ventricular hypertrophy which take into consideration rightward direction of the major electrical forces, albeit still posteriorly directed, are able to detect

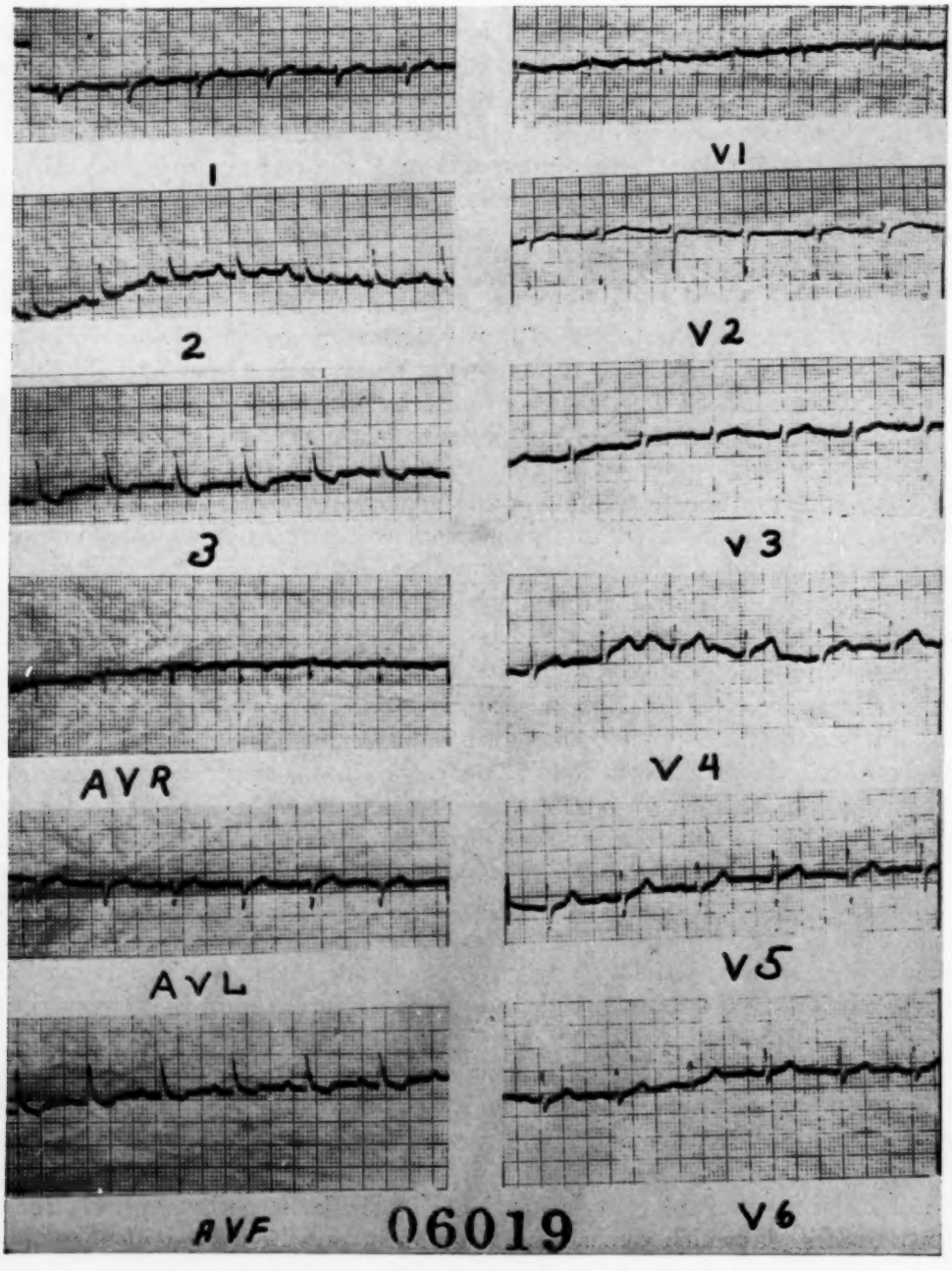

Fig. 2A.—Case 1. Tracing taken Oct. 4, 1956.

less advanced forms of the disease and lesser degrees of right ventricular hypertrophy. It is worthy of mention that, even in these fatal cases of decompensated cor pulmonale due to emphysema, the electrocardiogram in almost 30 per cent

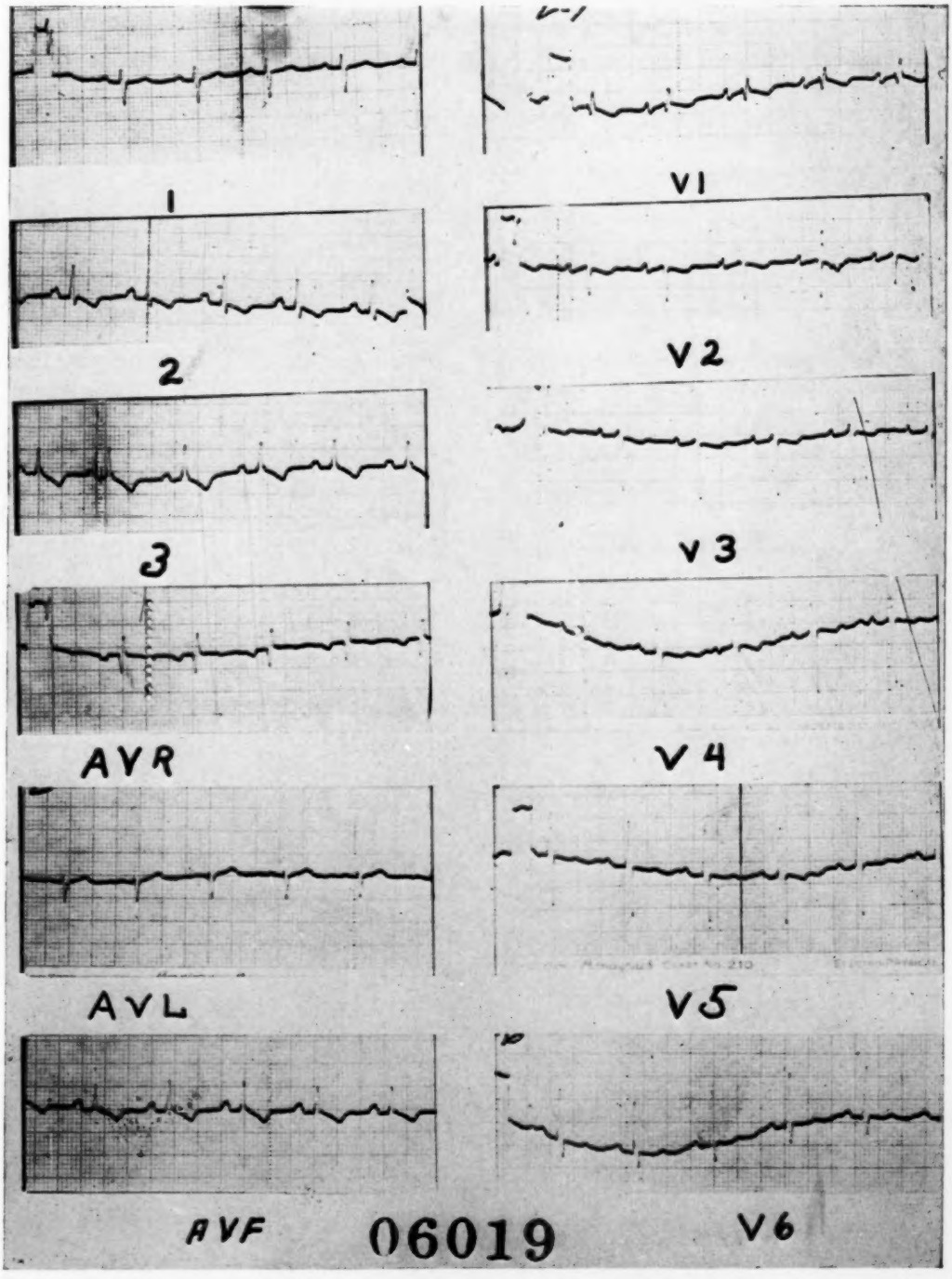

Fig. 2*B*.—Case 1. Tracing taken Nov. 10, 1956.

of the cases failed to indicate the presence of right ventricular hypertrophy by any of the criteria. Therefore, the ECG cannot always be used to supply diagnostic help in chronic cor pulmonale, even when the disease is far advanced and terminates in the death of the patient.

4. *Development of the picture of cor pulmonale in the ECG of patients followed with several tracings:* There were 4 patients in whom it was possible to follow

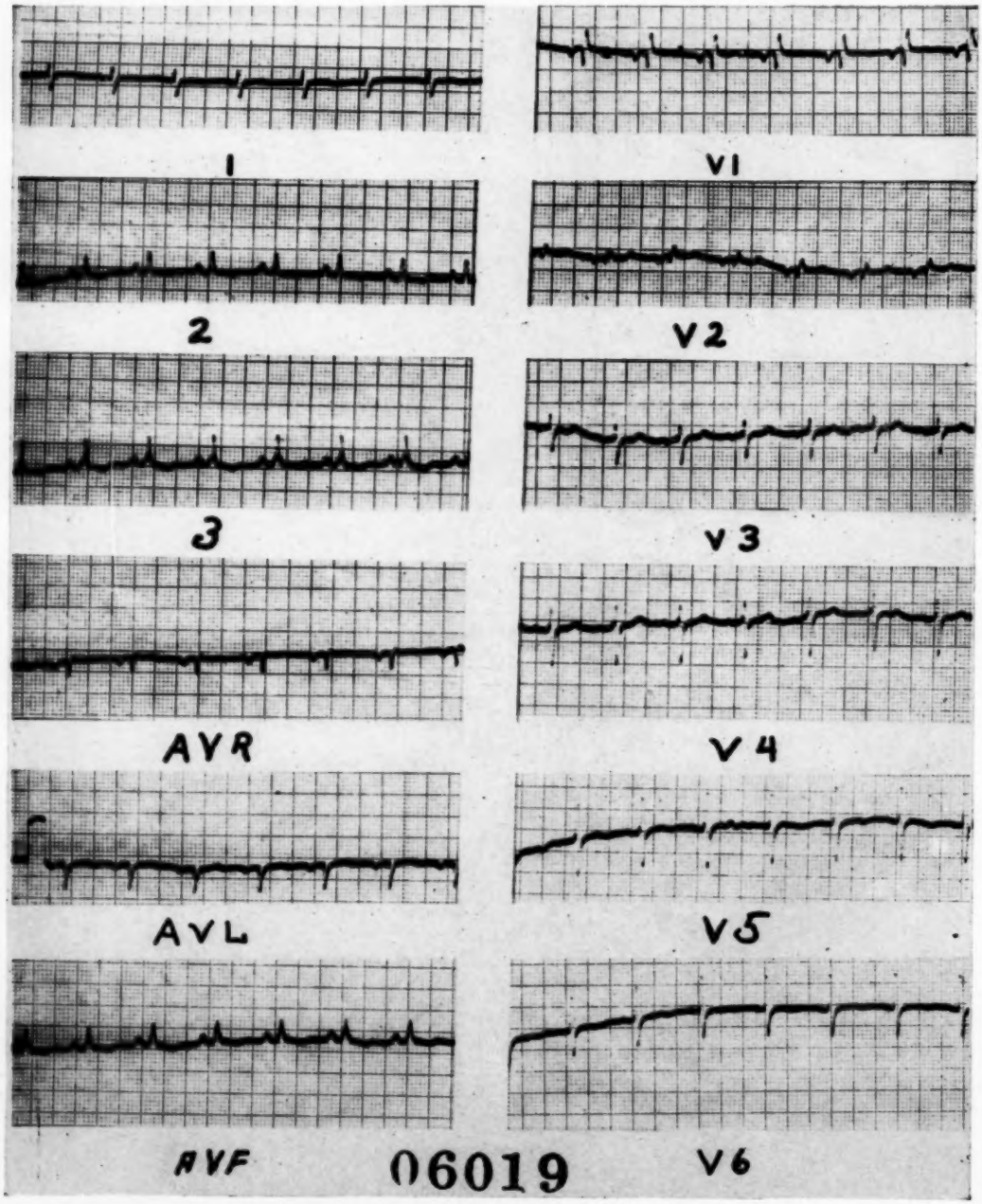

Fig. 2*C*.—Case 1. Tracing taken Jan. 11, 1957.

the development of the ECG pattern of right ventricular hypertrophy. In each patient, previous ECG tracings had been taken within the 6-month period prior to the final tracing. In each instance the earlier tracing showed a rightward but posterior direction of the major electromotive force (which would have satisfied the criteria of Sokolow and Lyon and of Milnor). Only later, in the more advanced stages of the disease, were there tall R waves over the right precordium, with the major electromotive force directed rightward and anteriorly rather than posteriorly (thus satisfying all sets of criteria). In 1 patient (Case 1) there was an intermediate type of tracing which resulted in an RSR pattern in the right precordial leads.[14] Two examples of the progression of changes described in the 4 patients are shown in Figs. 2 and 3.

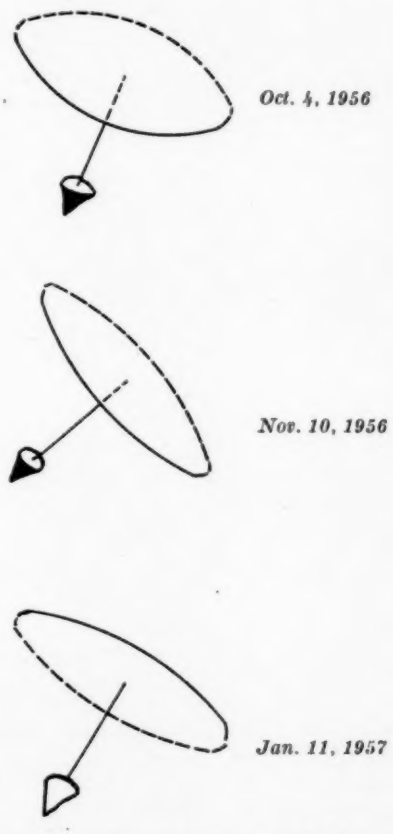

Fig. 2*D*.—Case 1. Progression of mean spatial vector (QRS) in patient with cor pulmonale.

Other Pertinent Clinical and Autopsy Data in the 18 Cases of Cor Pulmonale Secondary to Pulmonary Emphysema.—

1. *Clinical data:* The age of the group ranged between 46 and 76 years; all but 2 patients were in the span from 52 to 64 years. Various occupations were represented. However, only in one instance could the patient be said to have been employed in the "dusty trades" (Case 5, a foundry worker who did not show silicosis at autopsy). While industrial air pollution did not seem to

be a common finding in the environment of the group, all patients were cigarette smokers using from one to three packs per day over many years. A background of respiratory symptoms in the form of chronic productive cough with sputum

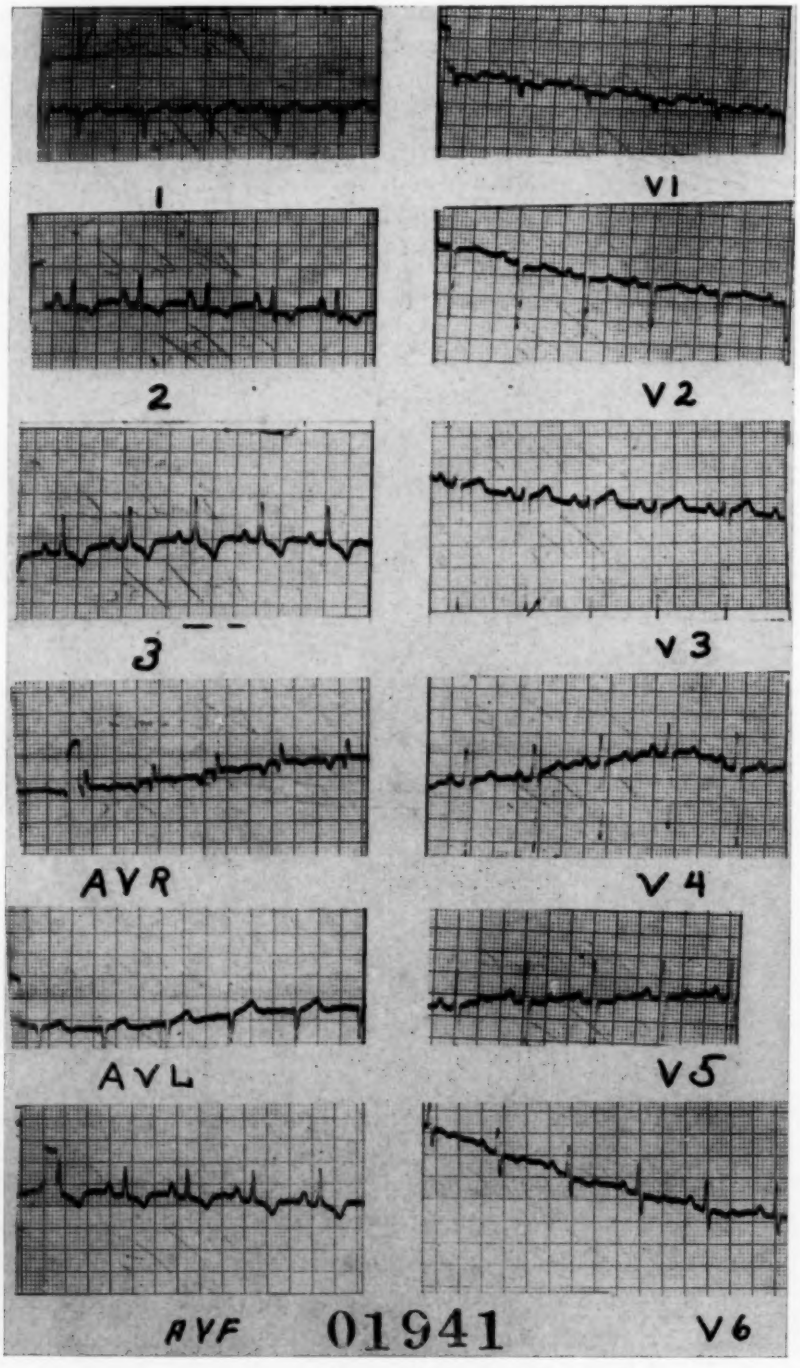

Fig. 3A.—Case 7. Tracing taken March 9, 1956.

was present in every case, and 6 of the 18 patients had a definite history of pneumonia. None of the patients had a history of allergic bronchial asthma, in the sense of recurrent attacks of wheezing of a seasonal nature, related, as far as could be determined, to external allergens. (The fact that the population being studied was comprised entirely of veterans would tend to exclude such patients, who would often have been screened from entering the Armed Forces.)

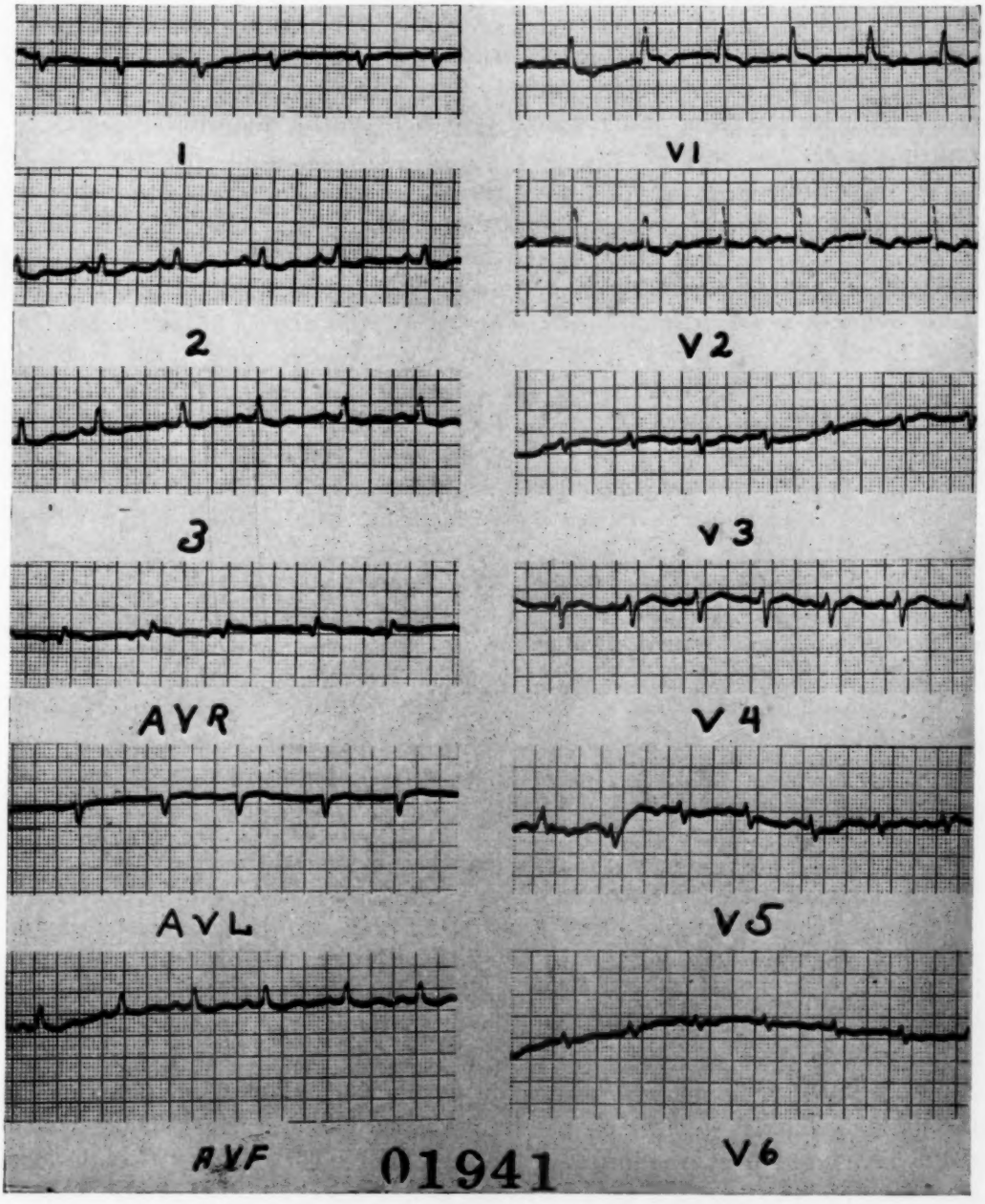

Fig. 3*B*.—Case 7. Tracing taken April 7, 1956.

Physical findings will not be dealt with in detail, as those of emphysema and pulmonary insufficiency are well described in the literature. None of the group had systemic arterial hypertension. As is often the case in right ventricular disease and emphysema, clinical detection of cardiomegaly was difficult.

Laboratory data pertaining to secondary polycythemia and respiratory acidosis is listed in Table II. The blood studies were venous, because arterial gas analysis was not available. Approximately half of the 18 patients had polycythemia, and almost all had elevation of the venous blood carbon-dioxide determination. Better data are available elsewhere[5] in regard to these aspects of pulmonary insufficiency, and the present figures are given for the purpose of correlation with the other findings in these patients rather than for a discussion of them per se.

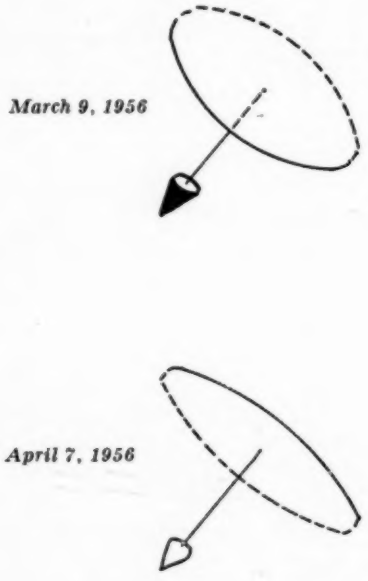

Fig. 3C.—Case 7. Progression of mean spatial vector (QRS) in patient with cor pulmonale.

2. *Pertinent autopsy data:* All patients had increased thickness of the right ventricular wall, and hypertrophy of muscle fiber was frequently noted microscopically. The presence of other types of heart disease is of interest because some investigators[5] have questioned whether cor pulmonale by itself will result in heart failure unless complicated by other heart disease. Of the 18 patients there were only 2 with significant additional anatomic heart lesions; Case 2 had aortic valvular stenosis (but his ECG showed right ventricular hypertrophy), and Case 11 showed patchy fibrosis of the myocardium. In the group as a whole the coronary arteries were widely patent and showed an occasional plaque, which did not seem to narrow the lumen of the vessels. No coronary vessel occlusions were found in any case, nor were there any other patients with evidence of myocardial or valvular lesions other than the ones mentioned. Thus, anatomically, it seems clear that cor pulmonale and heart failure may exist without additional

cardiac lesions being present. The weight of the hearts and measurements of the thickness of the right and left ventricles are listed in Table II. The increase in the thickness of the left ventricle in 6 of the patients has been a matter of discussion in cor pulmonale.[6,a,b]

Severe pulmonary emphysema was present in every patient. Of interest was the presence of chronic bronchitis in all patients but one who had saccular bronchiectasis. This is in agreement with previous studies of our group.[15] Pulmonary artery atheromata were commonly noted.

COMMENT

The correlation of the serial electrocardiograms with the clinical and autopsy data in this series of patients indicates the natural history of the development of the ECG findings in chronic cor pulmonale due to pulmonary emphysema. In the group of middle-aged adults in whom the problem is most frequently seen, it is usual for the major electrical forces of the ECG to be directed toward the left and posteriorly, presumably because of the preponderance of the left ventricular potential.[16] This is different from that which is seen in the infant or young child in whom there is manifest a proportionally greater dominance of rightward direction of electromotive force in the ECG.[13] The development of right ventricular hypertrophy in the infant with congenital heart disease thus presents, from the beginning, a situation electrocardiographically different from that of the middle-aged adult with emphysema and cor pulmonale. That is, rightward orientation of forces would be expected to occur with greater ease. This seems to be the case, since in children having congenital heart lesions with overload of the right ventricle there is a greater percentage of electrocardiographic evidence of right ventricular hypertrophy than in adults with emphysema heart disease.[11] There are other reasons, such as the level of the right ventricular and/or pulmonary artery pressures which often exceed those usual in emphysema.[17] These may account for the greater reliability of the ECG in congenital heart disease, and make consideration of the problem of emphysema heart disease separate from other causes of right ventricular disease.

The evidence presented indicates that the patient with decompensated cor pulmonale may follow one of several courses to death. He may die before the ECG indicates evidence of right ventricular hypertrophy and before his heart develops massive right ventricular thickening, or he may live long enough for clear evidence of right ventricular hypertrophy to occur and the right ventricular wall to become massively thickened. Obviously, there are all gradations between these extremes, as is seen in the correlation of ECG and heart weight in Table II.

Evidence is presented of a pattern of progression in the development of ECG changes of cor pulmonale and right ventricular hypertrophy, which is dependent on the stage of the disease when the patient is seen. This was illustrated in the progression of changes in 4 patients, and the gamut of changes in the group as a whole when the ECG was correlated with heart weight. In those without ECG evidence of right ventricular hypertrophy the major electromotive force was directed to the left and posteriorly (Cases 11, 13, 14, 16, and 17). Those who develop further changes show next a more rightward direction of the mean spatial

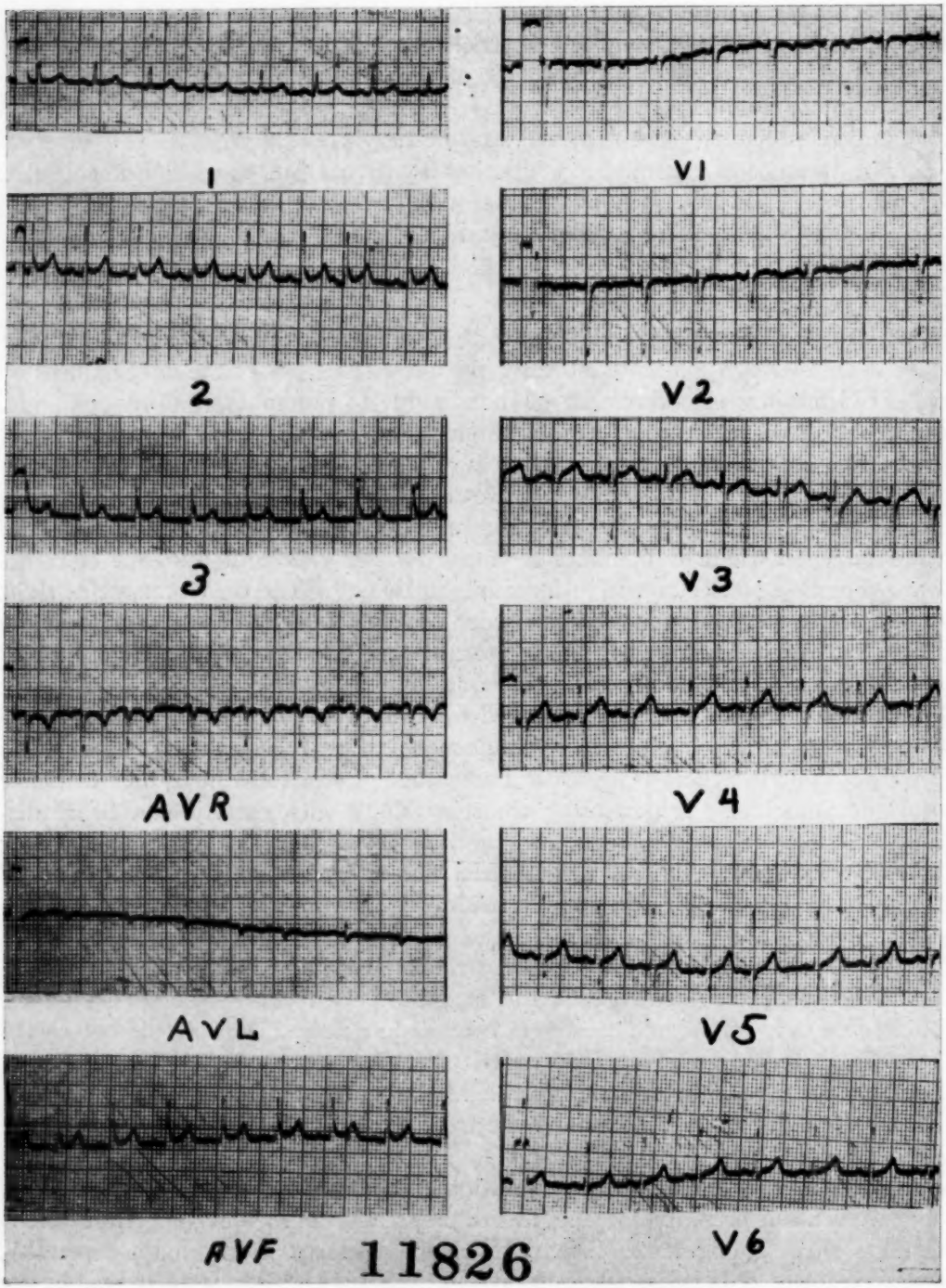

Fig. 4*A*.—Case 18 illustrates Stage 1 in the occurrence of the ECG picture in chronic cor pulmonale. The patient was a 60-year-old machine shop foreman, who gave a history of chronic productive cough for many years, and who died in severe right heart failure. Autopsy showed chronic bronchitis, pulmonary emphysema, and cor pulmonale, with the right ventricle measuring 8 mm. in thickness. The ECG is not diagnostic of right ventricular hypertrophy. The mean spatial vector is directed to the left and posteriorly.

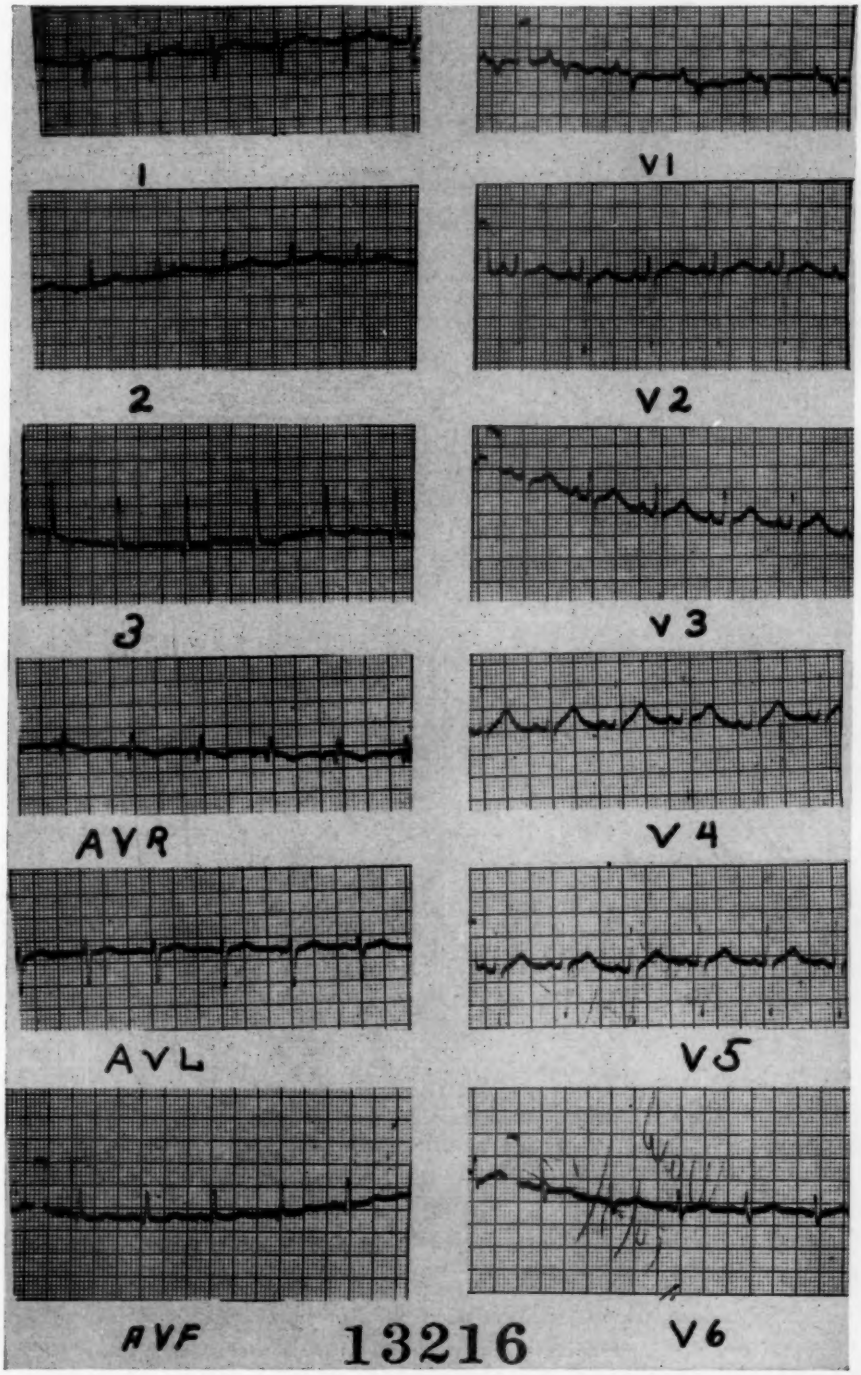

Fig. 4*B*.—Case 4 illustrates Stage 2 in the development of the ECG changes in chronic cor pulmonale. The patient was a 58-year-old male textile worker, who had a chronic cough for years. He died in congestive heart failure. At autopsy, chronic bronchitis, pulmonary emphysema, and cor pulmonale were found. The right ventricle measured 9 mm. in thickness. The ECG tracing shows the QRS mean spatial vector to be directed to the right and posteriorly.

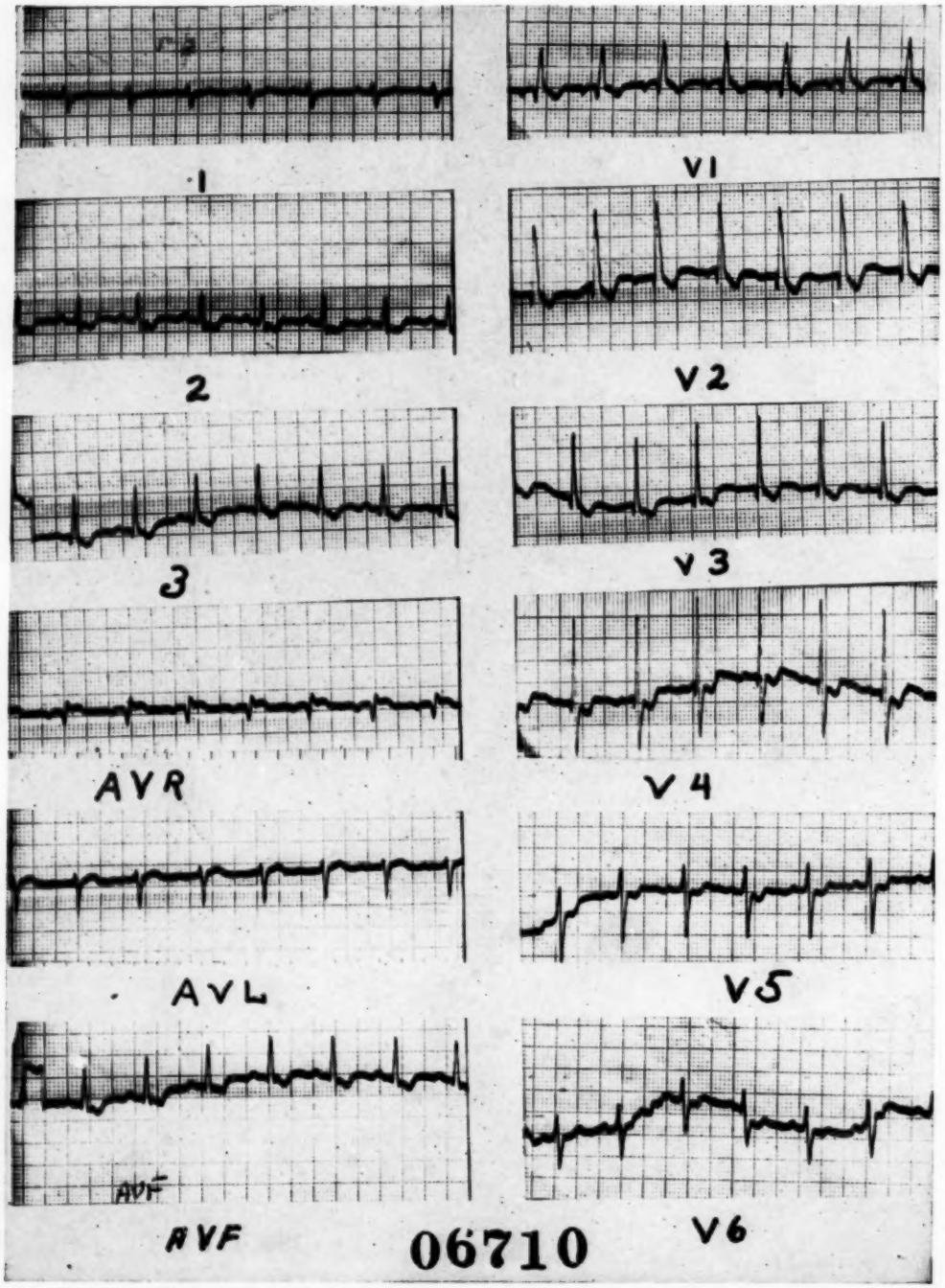

Fig. 4*C*.—Case 2 illustrates the most advanced ECG picture of chronic cor pulmonale, in which the mean spatial vector of the QRS is oriented both to the right and anteriorly, resulting in prominent R waves over the right precordial leads. The patient, a 62-year-old worker in a plastics factory, had clinical and autopsy evidence of emphysema and cor pulmonale.

vector, which then becomes directed to the right, albeit still posteriorly oriented (Cases 4, 6, 10, 12, 15, and 17). In the far advanced case with the severest disease the vector then becomes anteriorly as well as rightwardly oriented (Cases 1, 2, 3, 5, 7, 8, and 9). Special leads, such as V_{3R}, and vectorcardiography using the cube-type system seem consistent with this concept[7,11,18] which is diagrammatically pictured in Fig. 4*D*, with representative ECG tracings shown in Fig. 4 *A-C*.

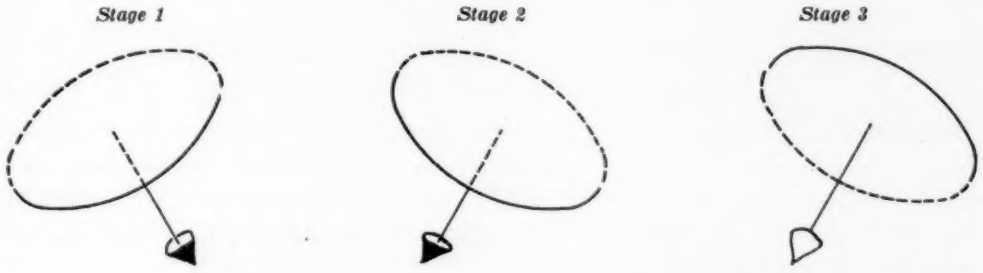

Fig. 4*D*.—Progression of change in the mean spatial vector of the QRS in cor pulmonale (representative change). Stage 1 (5 cases). Stage 2 (6 cases). Stage 3 (7 cases).

Electrocardiographic criteria for right ventricular hypertrophy then take on a more logical meaning. If, rather than attempting to memorize a complex set of patterns, one keeps in mind the previously described chain of events, one can predict which set of criteria will detect each phase of the ECG changes and understand what each criterion is attempting to delineate. The pattern of incomplete right bundle branch block will not be the source of confusion that is claimed by some.[11] We have been impressed by the relatively simple criteria of Milnor,[9] which take into consideration both of the major changes in the natural history of the ECG (the rightward as well as the anterior change in the major electromotive forces). As can be seen, there were as many cases in this series detected by Milnor's criteria as by the more complex and numerous criteria of Sokolow and Lyon.

It is furthermore noted and emphasized that no matter whose criteria are employed, a substantial number of patients with cor pulmonale will be missed by ECG. In our series of advanced terminal cases there were about 30 per cent who did not show evidence of right ventricular hypertrophy. This was simply because there had not been a sufficient change in the major electromotive force to produce enough change in the ECG to be diagnostic of right ventricular hypertrophy. Attempting to detect this group by adding further criteria will only result in including a large number of normal persons.

The clinical data again bring into focus several findings which have occurred with regularity in our previous studies[1a,15] on the problem of emphysema and would seem to give them added weight. These findings are a history of chronic cough with sputum, and the evidence at pathologic study of chronic bronchitis. The etiology of the cough and chronic inflammation of the bronchial tree could not be ascribed to industrial or residential environmental air pollution, in view of the diverse locations of occupation and residence of the group. All, however,

had been moderate-to-heavy cigarette smokers for many years. The thesis is again presented that the irritative effects of inhalation of cigarette smoke on the bronchial tree is associated with chronic bronchitis and bronchiolitis, which after years results in pulmonary emphysema. Other factors, such as infection or other forms of air pollution, may play a role in some instances, or may perhaps be the chief determining influence. However, it is our feeling that while cigarette smoking may not be the only cause of chronic bronchitis and emphysema, it is, in our experience, the most common etiological agent.

SUMMARY AND CONCLUSIONS

1. The electrocardiograms of 18 patients who had decompensated chronic cor pulmonale secondary to pulmonary emphysema, and in whom the diagnoses were proved by autopsy, are presented for analysis. Certain pertinent clinical and autopsy data are included. The ECG tracings were studied for the presence of P-pulmonale and right ventricular hypertrophy, using the criteria of Grishman, Milnor, Scott, and Sokolow and Lyon.

2. Evidence of P-pulmonale was found in 20 per cent of the patients. The ECG tracings satisfied the criteria for right ventricular hypertrophy in from 38 to 72 per cent of the cases, depending on which criteria were employed.

3. From the study of serial tracings in 4 patients, and from autopsy correlation of the ECG in the group of patients as a whole, a pattern of evolution of the electrocardiogram in cor pulmonale is presented. This pattern of development occurs in three stages. The first and earliest stage shows no deviation from the normal ECG, the major electromotive force being directed leftward and posteriorly. This was seen in 5 patients who died of decompensated cor pulmonale, with the ECG presenting a normal pattern. Their hearts tended to show the least evidence of increased weight and right ventricular thickening, as compared with the rest of the group. The second stage in the evolution of cor pulmonale is the development of a rightward direction of the major electromotive force, which, however, still remains posteriorly oriented. This produced a rightward direction of the axis in the frontal plane and a prominence of S waves in the left precordial leads, but no prominent R waves in the right precordial leads. The third and final stage is characterized by an anterior as well as rightward direction of major electromotive force. Patients in this category had the heaviest hearts with the thickest right ventricular walls. The ECG in these patients showed tall R deflections over the right chest leads as well as rightward orientation of the axis in the frontal plane.

4. In the 4 patients in whom it was possible to follow the progression of chronic cor pulmonale both clinically and electrocardiographically, the evolution progressed through the stages which have just been outlined.

5. The success of various criteria in the detection of right ventricular hypertrophy depends directly on which stages of the evolution of cor pulmonale the criteria encompass. Those which require the changes depicted in stage three dealing with anterior orientation of the major electromotive force detect fewer cases than the criteria which require changes in stage two as well as stage three. Clearly, no criteria would detect the right ventricular hypertrophy found at au-

topsy in those patients with cor pulmonale and normal electrocardiograms, which in this series of 18 cases amounted to about 30 per cent.

6. The associated findings of chronic bronchitis, chronic cough, and cigarette smoking were discussed in terms of the etiology of pulmonary emphysema.

I wish to thank Mrs. Rebecca Rinaldi, secretary to the Chief of the Medical Service, for her assistance in typing the manuscript.

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The Endocardial Lead in Complete Right Bundle Branch Block

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INTRODUCTION

Endocardial electrocardiographic studies were undertaken in our laboratory in an attempt to differentiate between the electrocardiographic patterns ascribed to right ventricular hypertrophy[1] and right bundle branch block.[2] In a previous study of 50 cases of congenital and acquired heart disease[3] this objective could not be accomplished by the use of an intracavitary lead. It was shown at that time that similar endocardial patterns occurred in patients with normal electrocardiograms and in those with electrocardiographic criteria for right ventricular hypertrophy, and incomplete right bundle branch block. Likewise, similar patterns were observed in patients with a variety of congenital and acquired lesions and in those with normal hearts.

During the original study, however, an unusual ventricular complex was observed in a patient with complete right bundle branch block. Hence, investigation of the intracavitary patterns was undertaken in a larger group of patients with conduction delay of at least 0.12 second or greater.

The findings obtained in this group are considered of sufficient interest to be reported, particularly since they may contribute to a theory for septal depolarization in bundle branch block.

MATERIAL AND METHODS

Twelve patients with complete right bundle branch block according to the electrocardiographic criteria of Wilson and associates[2] were studied. In addition, in 9 patients right ventricular hypertrophy was suggested by an R′ in Lead V_1 greater than 10 mm., as proposed by Barker and Valencia.[4] The etiology of the block was variable. In 1 patient it was apparently produced following repair of a ventricular septal defect 2 years previously. In another patient with an atrial septal defect and incomplete right bundle branch block, transient complete bundle branch block developed during cardiac catheterization. Congenital or acquired heart disease was present in all but 1 patient in whom idiopathic right bundle branch block was diagnosed.

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In order to eliminate confusion in the descriptions of the endocardial patterns, the following terminology was adopted. A positive deflection, whether reaching the isoelectric line or not, was termed an r or R wave, the first such deflection being an r, the second r′, the third r″, etc. A negative deflection was similarly designated s or S, s′, etc. These designations do not correspond, therefore, to the usual clinical terminology but are useful for clarification and interpretation, the important factor being the presence of a positive or negative deflection.

Right heart catheterization was performed in the usual manner employing a Cournand electrode catheter. The electrode tip was situated 1 mm. from the end of the catheter. Simultaneous recordings of the endocardial electrocardiogram, right heart pressures, and Lead V_{4R} or Lead II of the peripheral electrocardiogram, were obtained. Endocardial leads were obtained in the pulmonary artery, right ventricular outflow, mid, and tricuspid areas, and in the low right atrium. Recordings were made also during pullback of the catheter across the pulmonic and tricuspid valves. Tracings were recorded on a photo-oscillographic unit* or polyoscillograph† with sensitivity adjusted so that 1 mv. equaled 10 mm. of deflection. Known changes in sensitivity and varying paper speeds were made for more accurate study of the tracings when necessary.

RESULTS

The endocardial patterns obtained in the main pulmonary artery showed the following patterns: rSr′, RSr′s′, Qr, R, and an rS. When an rS was present, the S was usually notched or slurred on its ascending limb, corresponding in time to the r′.

The right ventricular endocardiogram showed an initial r in all patients, including 2 patients with a qR in Lead V_1. Following this initial r wave, one or more positive deflections were recorded in one or all ventricular positions in every patient. In order to identify more clearly this second or even third positive deflection, the patterns were compared in timing with the simultaneously recorded Lead V_{4R} or Lead II. Thus, a late positive deflection was seen in 7 patients, corresponding in time to the peak of the R′ or late R (rsR′, rR′, qR) in Lead V_{4R} (Fig. 1,*A*) or to the s(Rs) in Lead II (Fig. 1,*B*). In 3 of these patients this late positive deflection was an r″, and in 1 patient it was an r‴ (Fig. 1, *C* and *D*). In 4 additional patients a similar late R(QR) or R′ (rsR′) was seen in the low right atrium, where it was not observed in the ventricle in any position (Fig. 2,*C*). The endocardial late positive deflection, although observed especially in the outflow and/or tricuspid areas, was recorded also in the mid right ventricle in 3 patients.

Following the initial r deflection, an R′, r′, or r″, which was early or intermediate as judged by timing with the simultaneously recorded Lead V_{4R}, occurred in 9 patients (Fig. 1, *D*, *E*, and *F*). In 4 of these patients at least two early positive deflections, which were occasionally of considerable magnitude, were observed before the final late R (Figs. 1,*D* and 2). The early positive deflection was seen in all ventricular positions in 6 patients, in the outflow and mid areas in 1, in the tricuspid position in 1, and over the pulmonic and tricuspid valves in 1. Correlation with the peripheral lead revealed the early endocardial deflections to occur with the ascending limb of S or the ascending limb of R′ in Lead V_{4R} (rSR′). These multiple positive deflections in the endocardial lead were often reflected in notching of the late R or a double peaked R in Lead V_{4R}.

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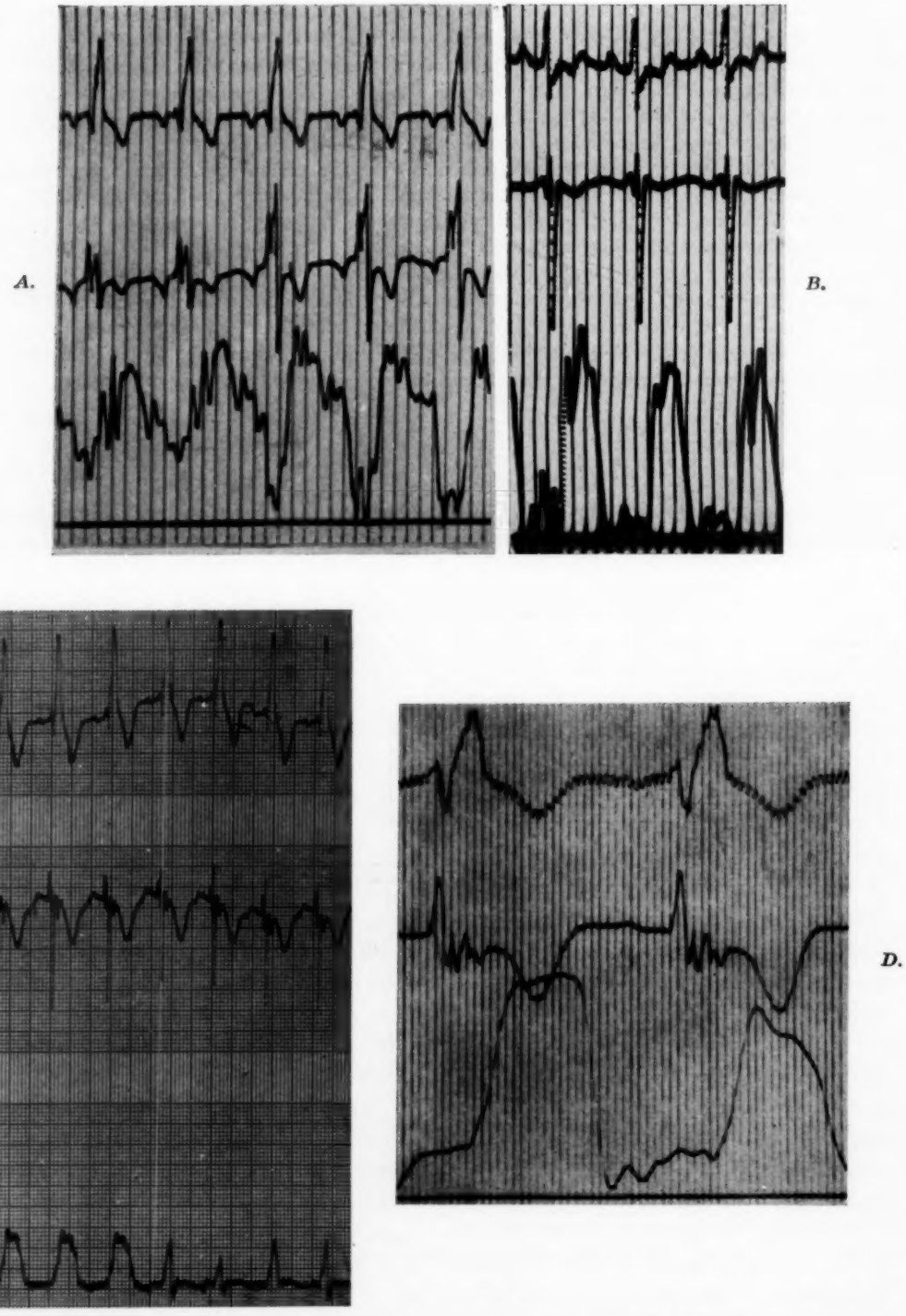
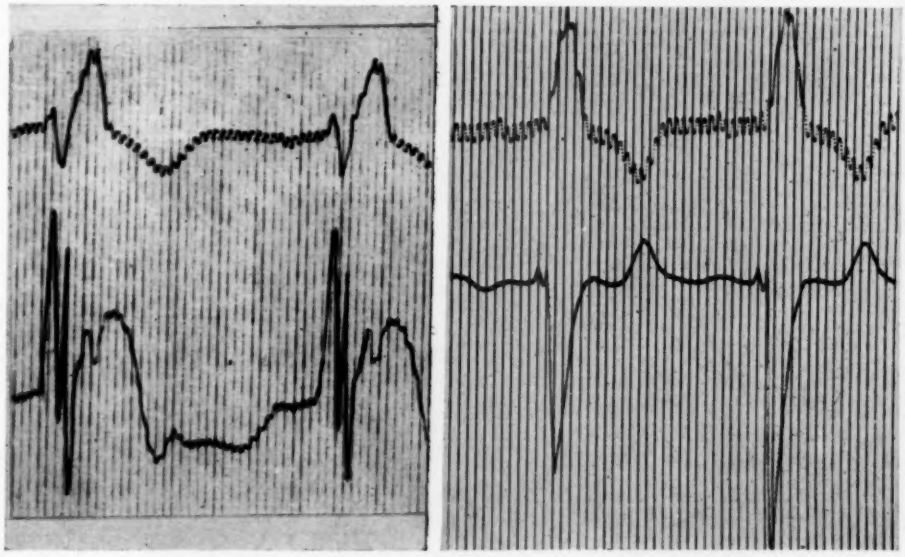


Fig. 1.—Right ventricular patterns obtained in patients with complete right bundle branch block. Lead V_{4R} (above; except in *B* where it is Lead II), endocardial lead (middle), pressures (below). Time lines 0.1 sec. in *A* and *B*, 0.04 sec. in *C*, and 0.02 sec. in *E*, *D*, and *F*. Paper speed 25 mm./sec. in *A*, *B*, and *C*, and 75 mm./sec. in *D*, *E*, and *F*.

In 2 patients tracings were recorded in the left ventricle when the catheter was passed through an atrial septal defect or ventricular septal defect. A QS and qRS were recorded, respectively.

Specific endocardial patterns could not be related to the underlying cardiac disease or to the varying mechanisms for the right bundle branch block in this group of patients. For example, similar intracavitary complexes were recorded in the patient with transitory block developed during cardiac catheterization, and in the patient in whom injury to the conducting tissue occurred following open heart suturing of a ventricular septal defect. Likewise, patients with mitral insufficiency or aortic stenosis with pulmonary hypertension, and one patient with idiopathic dilatation of the pulmonary artery and normal pulmonary pressure, showed similar ventricular patterns in the presence of complete right bundle branch block.



E. *F.*

Fig. 1, *E* and *F*.—*(For legend see opposite page.)*

DISCUSSION

The sequence of activation of the normal human heart is a subject of intensive investigation. Conflicting theories based on experimental work on the dog heart have been advanced. In particular, the activation of the interventricular septum has received much attention. The findings in the present study were unusual enough to stimulate further review of the subject, since it was felt that they might contribute to accumulating evidence concerning the activation pattern of the heart and, in particular, the ventricular septum.

In a previous study of 50 patients, utilizing endocardial leads,[3] only two positive deflections (rR′) were recorded within the right ventricle. In the present group of patients, however, there occurred between the initial r and the late r or R, one or more additional positive deflections. Although we are unable at

this time to assign a definite origin to these multiple intermediate positive deflections, a possible explanation may be proposed.

Although it is generally agreed that initial septal activation occurs from left to right at the level of the anterior papillary muscle, correlation of functional activity with the anatomy of the conducting system becomes difficult

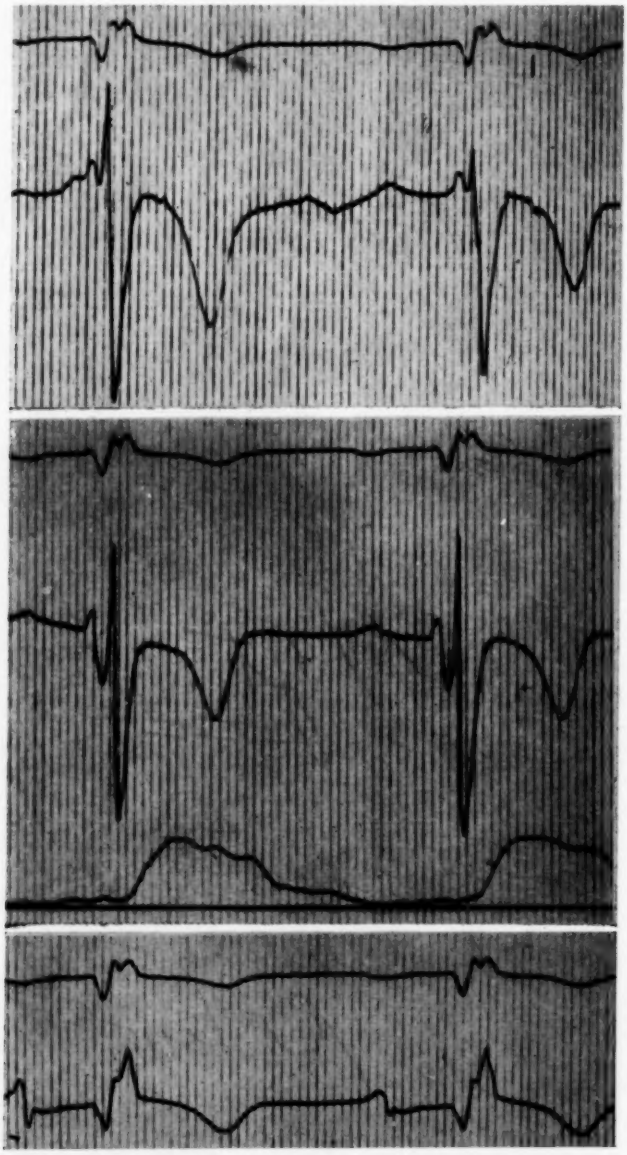


Fig. 2.—The early and late positive deflections of the endocardial pattern may be recorded singly or together in different areas of the right ventricle. Time lines 0.02 sec. Paper speed 75 mm./sec. Lead V_{4R} (above), endocardial lead (middle or below), pressures (below). Two different early positive deflections are recorded in the mid (*A*) and outflow (*B*) areas of the right ventricle, respectively, while the late positive deflection is recorded in the low right atrium (*C*) in the same patient. In another patient the early r′ is recorded in the mid right ventricle in *D*, while both the early r′ and late r″ are recorded in the infundibular chamber (*E*).

when the great variability in position, course, and branching pattern of the conducting tissue is appreciated. Anatomic studies of the conducting tissue of the heart reveal the existence of numerous small fibers from the A-V node,[5,6] common bundle,[7-9] and right and left bundle branches,[6,8] which directly enter the myocardium of the upper septum. It has been shown by Kistin[10] and by Truex and Bishof,[11] in a study of human hearts with interventricular septal defects, that the common bundle may vary in position and may lie under the

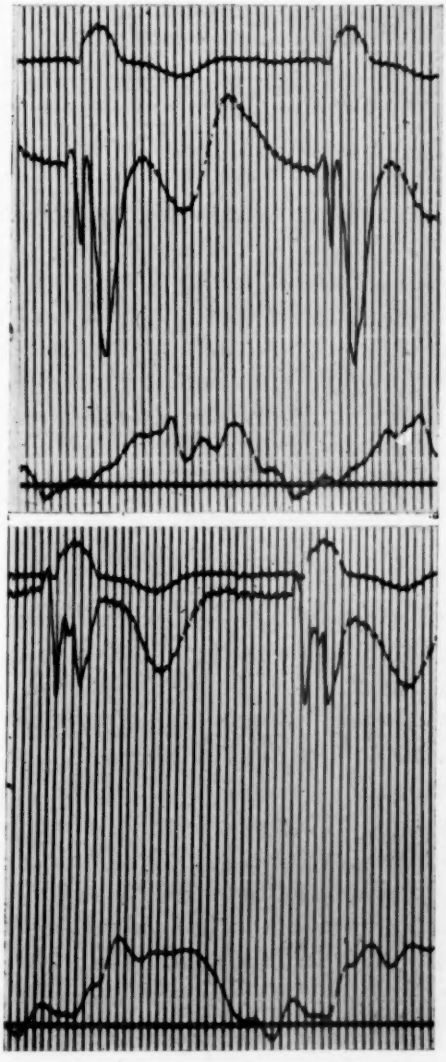


Fig. 2, *D* and *E*.—*(For legend see opposite page.)*

endocardium of the left or right side of the septum. Therefore, the course of the right bundle branch is also variable, either lying deep within the myocardium of the septum or traveling obliquely and deeply across the septal myocardium from the left to the right side before reaching the right endocardial surface.[11]

In 1 case (specimen 8) reported by Truex, the right bundle descended as two fascicles and never reached the right endocardial surface. In addition to the great variability of the conducting system the situation is further complicated by the fact that left and right septal muscle may extend to opposite sides of the septum, even to the opposite endocardial surface.[12-15] Too frequently it has been assumed that the septum is structurally divided into a distinct left and right side, whereas it is actually composed anatomically of intertwining fibers of left and right ventricular muscle spiraling obliquely through the septum. It is thus conceivable that in certain areas the right side of the septum may be activated by the left bundle branch.[12,15] It is generally agreed, therefore, that because of this great variability in the conduction system and muscular arrangement of the interventricular septum, measurements of activation time of various points on the endocardial surface cannot be considered an accurate method for investigating the timing and, thus, the sequence of activation.

More recently, however, investigators of this problem appear to agree at least upon the general movement of excitation in the septum from the apex toward the base.[12,15,16] Our previous studies with endocardial leads in the human heart are in accord with this concept.[3] An rS, recorded in the mid right ventricle, reflects initial activation of the lower septum from left to right, followed by depolarization of the left and right free ventricular walls; an RSR′S′, recorded above, over, and just below the pulmonic and tricuspid valves, reflects in the R′ and S′ later activation of the upper septum, followed finally by the upper free right ventricular wall, respectively. These right ventricular patterns were seen not only in patients with electrocardiographic evidence of incomplete right bundle branch block and right ventricular hypertrophy, but in patients with normal hearts and normal electrocardiograms as well (Fig. 3). The conclusion was reached, therefore, in agreement with previous work[17,18] that initial septal activation in right bundle branch block is similar to that in the normal heart. It was also suggested that later activation of the upper septum, represented by the R′ of endocardial leads, occurs normally as well as in right ventricular hypertrophy or right bundle branch block.

Thus, in patients with normal hearts, or with right ventricular hypertrophy, or with incomplete right bundle branch block, only two positive deflections are recorded within the right ventricular cavity. It is possible that only depolarization of large groups of septal muscle fibers is reflected in the intracavitary electrocardiogram when the total activation time is either within normal limits or only slightly delayed (less than 0.12 second). Thus, the endocardial r and R′ reflect only initial lower and late upper septal activation, respectively, and so correspond with the initial r and late R′, or initial r and ascending S of the precordial lead V_{4R}. We may assume that depolarization of the middle portion of the septum is not recorded by the intracavitary lead, or is obscured by the predominantly negative field created by depolarization of the free ventricular walls. In complete bundle branch block, however, with sufficient delay in conduction, it is possible that depolarizations of numerous areas on the right ventricular septal endocardial surface following initial depolarization of the lower septum are reflected in the multiple positive deflections in the endocardial lead. Abnormal

pathways of depolarization of the free ventricular walls have not been shown experimentally to exist. Kennamer and Prinzmetal,[19] utilizing plunge electrodes with two parallel lateral incisions about the electrode, showed no change in depolarization of the wall from endocardium to epicardium in the normal ventricle or in the ventricle with bundle branch block. Thus, it seems unlikely that intramural impulses could have contributed to the intracavitary positive deflections recorded.

Although the site of delay in right bundle branch block is not definitely known, experimental work seems to indicate that delay occurs either within the septum[17,20] or in both septum and free wall.[21] The present study may give additional support to theories of delay of the spread of activation through the septum—thus permitting the recording of multiple positive deflections within the right ventricular cavity. The relationship of the numerous small septal branches of

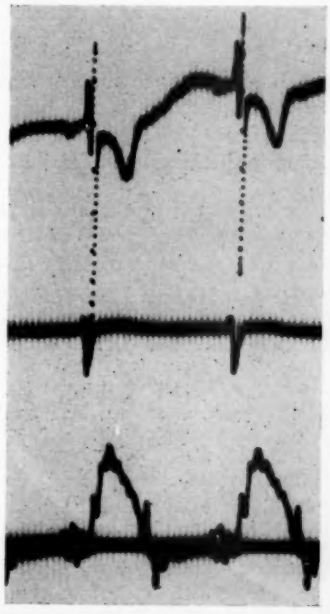


Fig. 3.—Illustration of the initial r and late R′ deflections in a patient with a normal electrocardiogram. Endocardial lead (above), Lead V_{4R} (middle), right ventricular pressure (below). Time lines 0.04 sec. Paper speed 25 mm./sec.

conducting tissue, mentioned above as arising from the common bundle or from the bundle branches themselves, to activation of various sites in the septum has not been investigated. Whether they are involved in the later activation of the middle and upper septum and in the intermediate positive deflections recorded by the endocardial lead can only be theorized. We can also only theorize as to whether the intermediate positive endocardial deflections are recorded because of delay in conduction (being obscured in the normal heart) or because, with deficiency of the right main bundle branch, conduction through other pathways, perhaps these small upper branches, becomes predominant.

It is not possible to extend a definite explanation for the present unusual findings. Suggestions have been made as to their possible origins. Further study in dogs is in progress in an attempt to evaluate some of the suggestions proposed above.

SUMMARY

1. Twelve patients with complete right bundle branch block have been studied by simultaneous endocardial and precordial leads.

2. Unusual patterns consisting of an initial r deflection, a late R′, and one or more intermediate and early positive deflections were recorded in the right ventricle.

3. The origin of the synchronous late endocardial and precordial R′ is attributed to late upper septal activation.

4. The origins of the early positive deflections cannot be stated definitely. It is suggested that they may be related anatomically to small branches of conducting tissue arising directly from the A-V node, common bundle, or upper bundle branches, and, functionally, to depolarization of the middle and upper septum.

The authors wish to express their appreciation to Dr. Alfred Pick for his helpful suggestions in regard to this manuscript.

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Electrocardiographic Cancellation: Some Observations Concerning The "Nondipolar" Fraction of Precordial Electrocardiograms

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Representation of the electromotive forces of the heart as a simple dipolar generator of electrical current is an interesting and useful concept which dates back to the earliest days of human electrocardiography.[1,2] Several reports published during the past few years indicate that within limits which are compatible with clinical application the electrical behavior of the heart during depolarization is, in fact, equivalent to a single, fixed-location current dipole.[3-5]

If this simple dipolar concept of heart-lead relationships is really correct, it might well serve as the basis for a number of corresponding simplifications in clinical electrocardiography. For example, the multitudinous leads that are currently employed could probably be abandoned in favor of three leads of special design which would portray accurately the transverse, longitudinal, and sagittal components of heart vectors. In the field of vectorcardiography such leads could be combined to yield accurate representation of equivalent heart vectors.[6,7]

Dipolar equivalency of the heart has been demonstrated qualitatively in a variety of ways, but attempts at strict quantitative evaluation of the concept have depended largely on studies of electrocardiographic cancellation. The technique of cancellation is a relatively simple one which has been described extensively in the literature.[8,9] As ordinarily performed, the cancellation procedure yields a series of values known as cancellation coefficients, which presumably express the "nondipolar" fraction of the electrocardiographic generator. Since cancellation coefficients are demonstrably small under a wide variety of conditions, it has been concluded that the equivalent cardiac concept is quite accurate.[3-5]

In opposition to this conclusion, direct studies of ventricular excitation indicate that the time-course of depolarization is a more complex process than the simple dipole concept could account for.[10-14] As we interpret such studies, the

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location of the equivalent cardiac dipole should shift during depolarization, and during some portions of the process two or more dipoles would be required for adequate equivalent representation.

The basic conflict arising from the two different types of experimental approach requires that at least one of them be critically re-evaluated. For this reason we conducted an earlier study[15] on esophageal electrocardiograms which suggested that good cancellation is not necessarily a reliable indicator of simple dipolar behavior of the heart, and which also provided some important clues concerning the true relation of cancellation to dipolar and nondipolar components of the electrocardiographic generator. Since the completion of the study on esophageal leads we have succeeded in developing some refined experimental methods for the investigation of cancellation in human subjects and in electrocardiographic models. Investigations performed with the improved techniques have enabled us to confirm the essentials, and greatly amplify the particulars, of our previous interpretation of the cancellation phenomenon. It is these investigations which form the basis of the present report.

OBSERVATIONS ON HUMAN SUBJECTS

Employing a modified form of Frank's four-electrode cancellation technique,[9] we compared the QRS complexes of Lead aV_R with numerous patterns derived from the apical portion of the precordium. Seventeen subjects selected from our teaching hospital population were thus studied. None of the subjects had clinically manifest heart disease except for one who was later found at necropsy to have invasion of the myocardium by giant follicular lymphoma.

The left arm and leg were joined by a 136,000 ohm resistor which had a center tap that served as a return terminal. The potential difference between the right arm and the return terminal was employed as the reference potential. The potential difference between the return terminal and a suction cup electrode of 1.5 cm. diameter located on the precordium served as the search potential. The right arm and the precordial electrode were joined by a calibrated 500,000 ohm potentiometer. The potential difference between the sliding contact of the potentiometer and the return terminal was the cancellation potential.

Both the cancellation and reference potentials were amplified by means of a Sanborn Vector Amplifier. After suitable attenuation through simple resistor networks the amplifier outputs were introduced into the direct-coupled input jacks of a Sanborn Twin-Beam Electrocardiograph, and recorded simultaneously at a paper speed of 75 mm. per second. The reference potential was recorded at the standard sensitivity of 1 cm. per mv., and the cancellation potential at a sensitivity of 5 cm. per mv.

With the subject lying on a comfortable bed in the dorsal recumbent position, the search electrode location and potentiometer setting were manipulated in the usual manner[8,9] until optimum cancellation was achieved. The quality of cancellation was monitored by means of a persistent-phosphor cathode-ray tube operating at a sensitivity of 10 cm. per mv. Optimum cancellation was then recorded with the subject breathing easily and naturally. Following registration of optimum cancellation, the search electrode was shifted to a number of different locations in the vicinity of the best location, and registration was accomplished for each of these locations with the potentiometer set at the position which produced the smallest peak-to-peak amplitude of the cancellation potential. However, these cancellation potentials were usually not recorded if the cathode-ray monitor failed to show the occurrence of complete cancellation at least twice during the QRS cycle.

A total of 175 such records were obtained from the 17 subjects. Cancellation coefficients were calculated from the formula

$$c = 10r/nR$$

where c is the cancellation coefficient in per cent, r is the peak-to-peak amplitude in millimeters

of the cancellation potential, n is the weighting factor of the reference potential as indicated by the potentiometer setting, and R is the peak-to-peak amplitude in millimeters of the reference potential.* The quality of cancellation was graded according to Schmitt's criteria[8] of a cancellation coefficient: 0 to 7.9 per cent, excellent; 8.0 to 11.9 per cent, good; 12.0 to 15.9 per cent, fair; 16.0 to 19.9 per cent, poor; 20.0 to 39.9 per cent, bad; 40.0 per cent or greater, no cancellation.

This phase of the study did not provide data suitable for strict quantitative analysis because the quality of cancellation tended to wax and wane with respiratory movements. However, it did prove most valuable in demonstrating that mirror electrocardiograms of fairly satisfactory quality can be obtained at a number of different search electrode sites on each of a significantly large number of subjects. It also confirmed our earlier prediction[15] that it should be a relatively simple matter to obtain complete cancellation at least twice during inscription of the QRS complex.

The times at which exact cancellation occurs depend intimately upon such factors as search electrode position, phasic variations due to respiration, and the potentiometer setting. In five sets of records the times of exact cancellation were carefully determined with respect to the instant of the peak deflection of the reference tracing. Fig. 1 illustrates one such analysis in graphic form. The bars indicate the various instants at which exact cancellation occurred for each of the search electrode sites which were tested. The lengths of the bars indicate the total variations in cancellation time which were due to respiratory effects. Even the most conservative interpretation of this bar diagram (namely, that the cancellation times indicated by the inner and outer ends of the bars occur at the same respective peaks of respiratory movements) indicates that complete cancellation may occur at numerous pairs of instants. This observation is in accord with previous predictions.[15]

It was also anticipated that the potentiometer setting should exert a strong effect upon the times at which exact cancellation occurred. This effect was observed in 2 subjects with respiration suspended at the end of normal expiration. The usual search procedure was then pursued until a small W-shaped cancellation complex was observed on the monitor screen. Under these conditions slight clockwise and counterclockwise rotation of the potentiometer produced an easily discernible widening and narrowing of the interval between the two moments of exact cancellation.

In order to obtain data which could be compared in a strictly quantitative manner, the cancellation procedure was repeated in 5 of the more cooperative subjects, with the breath held at the end of normal expiration. The validity of the suction cup device as a search electrode was also tested in 3 subjects by first recording optimum cancellation with the cup electrode, and then recording with a needle electrode located at the center of, and at six equally spaced points on the periphery of, the circular area which the cup electrode had occupied. In two cases the needle electrode technique produced cancellation potentials which were essentially the same in magnitude as, and very similar in form to, those obtained with the cup electrode. In the third case there were distinct differences between the various point locations tested. Interestingly enough, although the location of the search electrode was more critical in this third subject than in the other two, the quality of his cancellations was the poorest of the entire group.

The quantitative data derived from this phase of the study are presented in Table I. The best electrocardiographic mirror images were found, generally, on the chest wall in the vicinity of the conventional fifth and sixth precordial electrode positions. In all except three records exact cancellation occurred at least twice during the QRS cycle. In many records exact cancellation occurred three or four times, and in one record five moments of exact cancellation were observed during the inscription of the QRS complex. In two records exact cancellation did not occur, and in another record it was impossible to determine the multiplicity of exact cancellations because the small residual potentials were somewhat obscured by somatic tremor and power line interference.

One of the most striking features of the study was the relatively large number of search electrode sites which yielded mirror patterns of approximately the same quality. For example, in Subject No. 3 eight search electrode sites (approximately 16 square centimeters of body surface)

*This formula, although different in form from Schmitt's equation,[8] is virtually equivalent to it.

out of eleven which were recorded yielded mirror patterns of excellent quality. Fig. 2 shows the various search electrode sites which were tested on this subject. It also shows, for purposes of comparison, three of the best cancellations which were obtained.

TABLE I. COMPARATIVE STUDY OF LEAD aV_R WITH PRECORDIAL MIRROR PATTERNS

	SITE NUMBER	WEIGHTING FACTOR—POTENTIOMETER	CANCELLATION COEFFICIENTS (PER CENT)					CANCELLATIONS PER QRS
			EXCELLENT	GOOD	FAIR	POOR	BAD	
Subject No. 2	1	.60			15.2			4
	2	.64				19.5		4
	3	.63			14.9			2
	4	.64			15.6			4
	5	.65				18.7		4
	6	.67				18.4		4
	7	.67				17.5		4
	8	.65			15.4			4
	9	.49					34.1	3
	10	.53					27.3	4
	11	.68				19.7		2
	12	.72				18.4		3
	13	.78		11.9				2
Subject No. 3	1	.63	5.7					4
	2	.64	7.0					3
	3	.60	7.5					4
	4	.56		10.7				2
	5	.65		10.0				2
	6	.64	6.3					3
	7	.64	6.3					2
	8	.65	4.9					?
	9	.64	7.8					0
	10	.65		8.0				0
	11	.53	5.7					2
Subject No. 4	1	.56	4.9					2
	2	.57	6.7					2
	3	.53	5.2					3
	4	.54	4.7					3
	5	.54	5.9					3
	6	.56	5.2					3
	7	.57	7.2					3
	8	.52	7.6					2
	9	.54		8.3				3
	10	.46	4.5					2
Subject No. 9	1	.39			14.2			4
	2	.30				19.7		4
	3	.44					24.8	2
	4	.53	5.1					3
	5	.51	6.7					5
	6	.47		11.1				3
	7	.46		10.6				4
Subject No. 10	1	.57		10.9				3
	2	.60			13.4			3
	3	.53	7.9					3
	4	.50	6.5					3
	5	.48	7.5					3
	6	.61		11.4				4
	7	.51					35.2	4

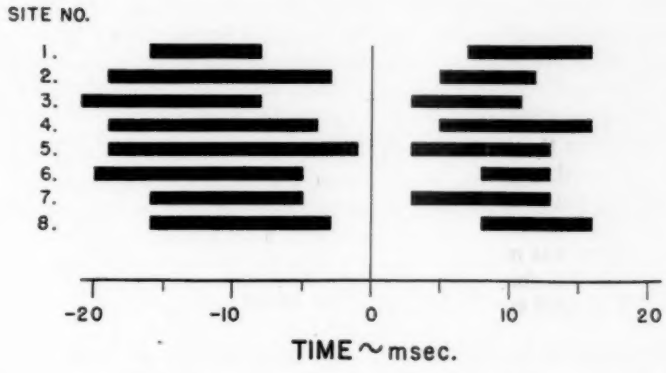

Fig. 1.—Analysis of times at which complete cancellation occurs when Lead aV_R is matched against leads derived from several locations on the apical precordium. Zero time refers to the instant at which the greatest deflection of Lead aV_R occurs. The horizontal bars indicate the instants at which complete cancellation occurred for each search electrode site tested. The lengths of the bars represent the total variation in cancellation times produced by normal respiratory movements. The analysis supports the theoretical prediction that complete cancellation of electrocardiographic mirror patterns should occur at numerous pairs of instants. (Further discussion in text.)

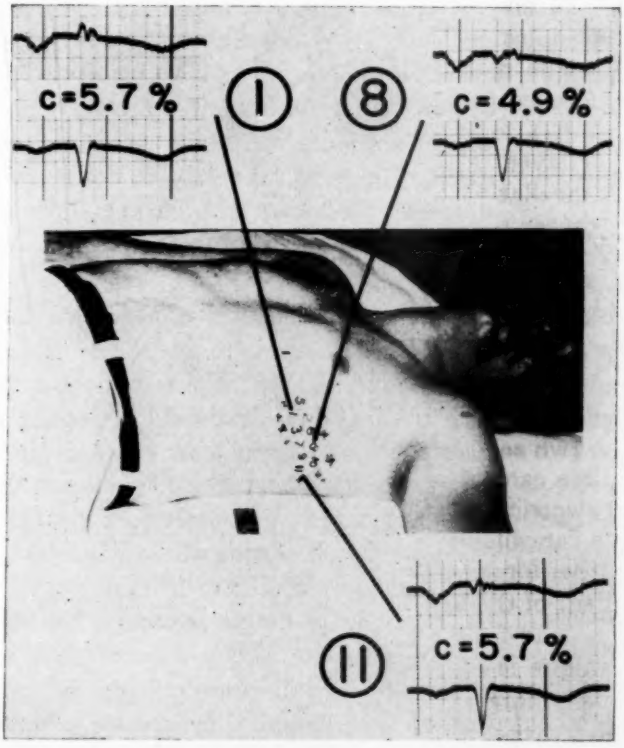

Fig. 2.—Illustration of the various precordial electrocardiographic sites which were compared with Lead aV_R of Subject No. 3. Excellent cancellations were obtained at Sites 1 through 3, 6 through 9, and at Site 11. Good cancellation was obtained at Sites 4, 5, and 10. The crosses indicate additional sites at which cancellations were tested, but not recorded because of inferior quality. The electrocardiographic cuttings show the three best results obtained. The upper tracing of each cutting is the cancellation potential recorded at five times standard sensitivity; the lower tracing is Lead aV_R recorded at standard sensitivity. Although Site 8 yielded the smallest coefficient, the phase difference of 0.02 second between the two tracings indicates that cancellation is totally lacking during approximately the initial one fourth of the depolarization phase.

In Subject No. 4 excellent cancellation was obtained at nine out of ten search electrode sites, in Subject No. 10 at three out of seven sites, and in Subject No. 9 at two out of seven sites. Subject No. 2 showed good cancellation (c = 11.9 per cent) with an unusually high-voltage mirror pattern occurring some distance from the usual mirror location. In the vicinity of the usual mirror location he showed fair cancellation in four out of twelve trials.

No systematic effort was made to correlate the cancellation of P and T waves with QRS cancellations. However, it was observed, as is illustrated in Figs. 2, 5, and 6, that conditions producing the best cancellation of QRS complexes are commonly attended by poor cancellation of P and T waves.

OBSERVATIONS ON ELECTROCARDIOGRAPHIC MODELS

The observed failure of the best image patterns of Lead aV_R to occur at a critically singular location (or at least on an extended, narrow locus, as would be the case with planar dipole loops[16]) is difficult to reconcile with the equivalent cardiac dipole concept of electrocardiographic genesis. Consequently, we investigated our alternative theory of cancellation[15] by means of fairly exhaustive observations performed on electrocardiographic models.

The basic principles of the alternative theory are illustrated by the model shown in Fig. 3. The model consists of a circular sheet of analog computing paper* with a reference electrode (R), a search electrode (S), and two return electrodes (E_1 and E_2), located as shown. The circular arcs (A′ and A″) represent the accession layer at two different instants during depolarization. The terminals of the cancellation connection are the sliding contact of the potentiometer (P) and the center tap of a large-valued resistor (not shown in the illustration) which joins the terminals E_1 and E_2. The curved lines within the model represent the cancellation lead field (plotted in isoflow intervals) as mapped out by a previously described technique.[17]

According to prior calculations the cancellation network should be completely insensitive to the electromotive forces represented by A′ and A″. The model confirms this prediction, since within the limits of technical error both accession layers lie between two zero-flow lines of the lead field. Consequently, the model shows how complete cancellation can occur at least twice during depolarization† even though the electrical center of the heart shifts significantly. In addition to producing double cancellation, the cancellation network tends to be insensitive to the electromotive forces of the heart during the remainder of depolarization because the gradient of the lead field is weak in the vicinity of its null point.[18]

Although the lead-field example of double cancellation shown in Fig. 3 is correct, the technique is of limited value because each set of conditions tested requires a relatively large amount of laborious calculation and technical procedure. In order to expedite the experimental procedure, we prepared a circular paper model, 30 cm. in diameter, in which accession layers were replaced by equivalent dipoles.

The semicircular electromotive surface, A′ + A″, of Fig. 3 was replaced by a

*Sunshine Scientific Instruments, Philadelphia, Pa.

†For the sake of convenience the phenomenon of complete cancellation at two different instants will be referred to hereafter as *double cancellation*. Cancellation at more than two instants will be referred to as triple, quadruple, or multiple cancellation, according to the requirements of the situation.

horizontally oriented dipole, D_1, located at the radius center of the semicircle. The interpolar separation of D_1 was 1.25 cm. A second dipole, with an interpolar separation of 1.0 cm., was constructed as a freely movable unit which could be located wherever desired on the model. In the actual conduct of the experiment the orientation of this dipole was maintained radial with respect to the

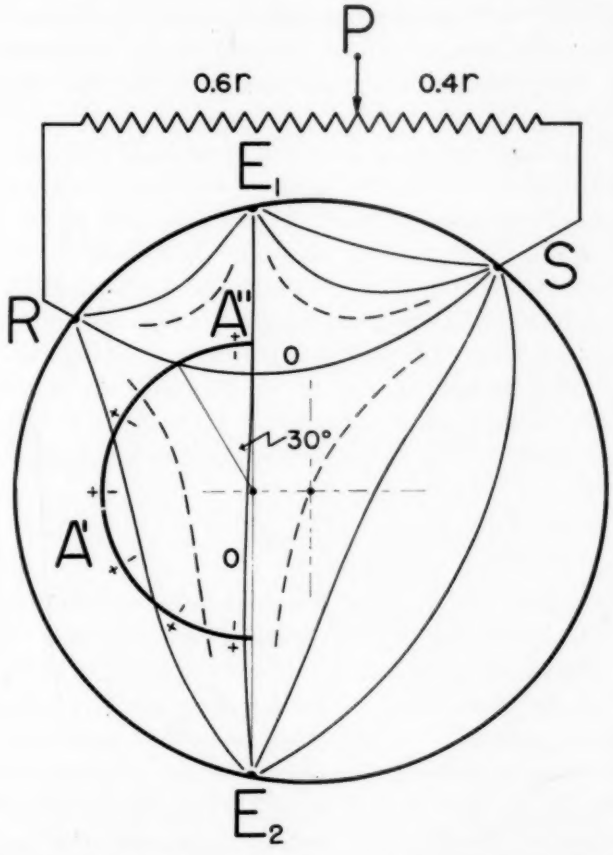

Fig. 3.—A specific example of the null-lead hypothesis of electrocardiographic cancellation as demonstrated in a plane, circular model. The sliding arm (*P*) of a potentiometer which joins the reference (*R*) and search (*S*) electrodes is one terminal of the cancellation network. The return terminal is the center tap of a large-valued resistor (not illustrated) which joins electrodes E_1 and E_2. The curved lines within the circular lamina are the lead field of the cancellation connection, plotted in isoflow intervals. The connection completely cancels out the potentials due to the accession layers (*A′* and *A″*), because each layer (except for small technical error) lies between two zero-flow lines in the lead field. The point at which the zero-flow lines intersect is the null point or electrical center of the cancellation connection.

center of D_1, and the model was tested with the center of the movable dipole systematically located at various locations within the semicircular area bounded by A′ and A″. The question of other orientations of the movable dipole is dealt with, in part, in the appendix.

With the two dipoles connected to the horizontal and vertical inputs, respectively, of a vectorcardiograph, the cancellation connection of the model was reciprocally energized by means of an alternating current of 5 cycles per second.

For a given position of the reference electrode and the movable dipole, double cancellation of the two dipoles was sought for by alternately shifting the search electrode position and adjusting the potentiometer setting until the vectorcardiographic beam became immobile.

Some of the results obtained with this model are illustrated in Fig. 4. The stippled area in the figure shows the various locations at which the radially oriented, movable dipole could be doubly cancelled with the fixed dipole when the reference electrode was located on the horizontal axis of the model. This particular placement of the reference electrode proved to be the most demanding of the various positions which were tested. In comparison, when the reference electrode was shifted 30 degrees away from the horizontal axis, double cancellation could be obtained with the movable dipole located over a decidedly more extensive range of area, as indicated by the crosshatched area in Fig. 4.

In addition to the large number of dipole combinations which proved susceptible of double cancellation, we were also impressed with the relatively small magnitude of the residual potentials obtained when the search electrode was located some distance from the position required for complete double cancellation. This observation agrees with the known fact that the gradient of a cancellation lead field is relatively weak in the vicinity of its null point (electrical center). Unfortunately, we failed to record this observation in a manner suitable for quantitative evaluation.

DISCUSSION

Although several factors may be responsible for nondipolar behavior of the electrocardiographic generator, the theoretical phase of this study was limited almost solely to the effects produced by translocation of a single equivalent cardiac dipole during depolarization. Having assigned a considerable variety of movements to the equivalent cardiac dipole, we still found it a relatively simple matter to obtain electrocardiographic cancellations of good quality. In other words, good cancellation does not necessarily bespeak relative immobility of the equivalent cardiac dipole center, and, consequently, does not necessarily support the validity of the simple dipolar concept.

Our reasons for this conclusion are exemplified by Fig. 3, in which A′ represents the accession layer at one instant during depolarization, and A″ the accession layer at a later time. The equivalent dipoles corresponding to these two instants are located at the midchordal points, respectively, of A′ and A″, and are radially oriented. As the depolarization forces shift from distribution A′ to distribution A″, it is apparent that the magnitude of the cancellation potential does not increase progressively. Instead, some cancellation potential begins to appear, then regresses, and disappears completely when distribution A″ is achieved. The return to complete cancellation will have occurred even though the equivalent cardiac dipole has moved through a distance which is equal to approximately half of the diameter of the model heart. It is also of some interest that the electrical center (null point) of the cancellation connection shown in the figure does not coincide with the "center of gravity" of the two electromotive surfaces under consideration.

The foregoing is a specific example of our previously proposed[15] null-lead theory of cancellation. According to the null-lead theory, electrocardiographic cancellation is readily obtained because complete cancellation is assured at numerous pairs of instants throughout the QRS cycle, and because the lead connection is inherently insensitive to electromotive forces occurring during the remainder of depolarization. Despite the simplicity of the models which we studied, theoretical considerations lead us to believe that the same principles apply with equal validity to electrically inhomogeneous volume conductors (that is, to the human body). A full treatment of these theoretical considerations is beyond the scope of this report, but they will be touched upon in the appendix.

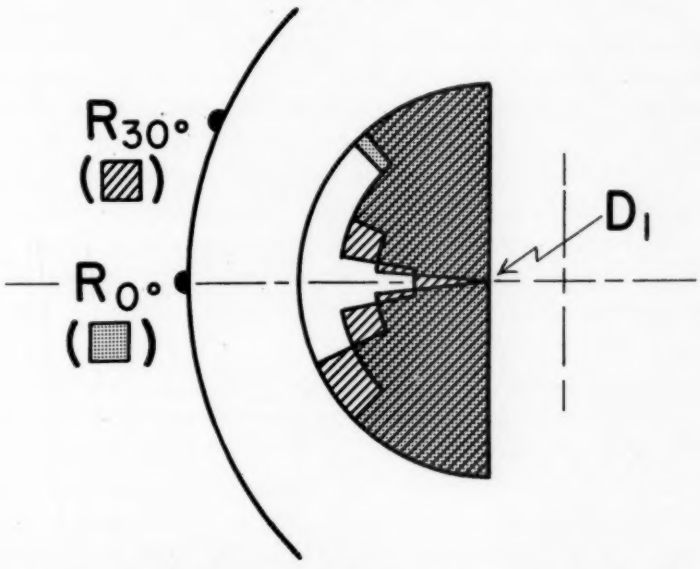

Fig. 4.—Pictorial illustration of the results obtained with a plane circular model which contained two equivalent cardiac dipoles. One of the dipoles was maintained in a fixed, horizontally oriented position at D_1. The second dipole was systematically placed at various positions within the semicircular area, with its axis passing through D_1. The return connection was the same as that employed in Fig. 3. With the reference electrode located on the horizontal axis ($R_0°$), cancellation conditions could be found which were completely insensitive to both the fixed dipole and the movable dipole when the latter was located anywhere within the stippled area. The corresponding area when the reference electrode was located 30 degrees away from the horizontal axis ($R_{30}°$) is indicated by the crosshatching. The model demonstrates that cancellation of two equivalent dipoles (double cancellation) can be obtained under a wide variety of conditions.

In conformity with the null-lead concept, our observations on human subjects verify that it is a simple matter to produce complete electrocardiographic cancellation at numerous pairs of instants during the QRS cycle. Actually, triple and even quadruple cancellations were not uncommonly observed. The occurrence of such multiple cancellations might seem to favor the simple dipolar concept, but it was noted that they tended not to occur in association with the smallest cancellation coefficients.

The observation that excellent image patterns may be found over a relatively large area of precordium also weighs against the idea that the location of the

equivalent cardiac dipole is essentially immobile. This observation is especially striking when one considers that a small displacement on the anatomic surface of the region which we explored is attended by a relatively large displacement on the electrocardiographic image surface. In contrast to the single, fixed-location dipole concept of electrocardiographic cancellation, the null-lead theory of cancellation more or less predicts the observed multiplicity of favorable search electrode positions.

Probably the most deceptive feature of equivalent dipole studies is the manner in which the data are quantitatively and qualitatively analyzed. For instance, the upper strip of Fig. 5 illustrates an example of excellent cancellation (c = 4.8 per cent). Simultaneous registration of Lead aV_R and its precordial mirror, shown in the lower strip, confirms that the two QRS patterns really are well matched. For purposes of comparison, Fig. 6 shows the corresponding tracings in a case of fair cancellation (c = 15.2 per cent). Other interpretations besides "fair cancellation" in the latter case might be that "85 per cent of the two QRS signals are identical in shape and phase," or that "no more than 15 per cent of the precordial QRS potentials are due to local, nondipolar influences." All of these expressions imply that the precordial electrocardiogram and Lead aV_R are acceptable mirror images of each other. Yet, simple inspection of the simultaneously recorded object and mirror patterns does not support such a conclusion, for it is apparent that the terminal deflections of the two QRS complexes are actually quite poorly matched.

The discrepancy between the favorable numerical value and the obvious mismatch of the two complexes is due to the type of calculations employed. Cancellation coefficients are computed on the basis of peak-to-peak amplitudes of deflection. Thus, in Fig. 6 the badly matched terminal deflections are lumped together with well-matched main deflections. The over-all result is "fair" cancellation, even though the precordial lead contains sizable potentials which have little counterpart in the reference lead.

The peak-to-peak cancellation coefficient may be misleading even in cases of excellent cancellation. An example of this is the cancellation of Lead aV_R which was obtained at precordial Site 8 of the subject illustrated in Fig. 2. Although this particular search electrode position yielded the smallest cancellation coefficient for the numerous locations which were explored, inspection of the tracings shows that the onset of the cancellation potential occurred approximately 0.02 second before the onset of the Lead aV_R deflection. This means that the best precordial mirror pattern contained a small Q deflection which had no counterpart in Lead aV_R, and that there was no cancellation (c = 100 per cent) during the inscription of the precordial Q wave. We do not know whether or not this completely nondipolar phase of the precordial electrocardiogram is clinically significant, but it is interesting to note that it occupies approximately one fourth of the entire depolarization process.

Perhaps nondipolar components of precordial leads are unimportant in the interpretation of normal electrocardiograms, but we doubt that they can properly be discarded in the consideration of abnormal states. The cancellation study which Schmitt and associates[19] performed on a group of patients with cardiac

abnormalities resulted in many coefficients of fair to poor quality. A similar study by Seiden and Keisman[5] produced a number of fair coefficients. If our contention is correct that "fair" cancellation is an overgenerous grading, it follows that the published cancellation data do not necessarily rule out the importance of nondipolar (local influence) factors in the genesis of abnormal precordial

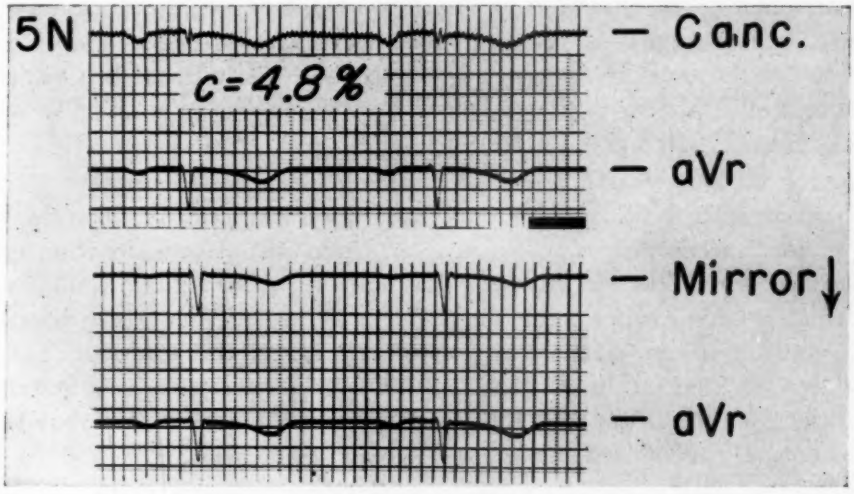

Fig. 5.—An example of excellent correspondence between Lead aVR and its best precordial mirror pattern. The cancellation coefficient is small, all deflections of the QRS complexes appear well matched with respect to form and amplitude, and virtually no phase shift is present.

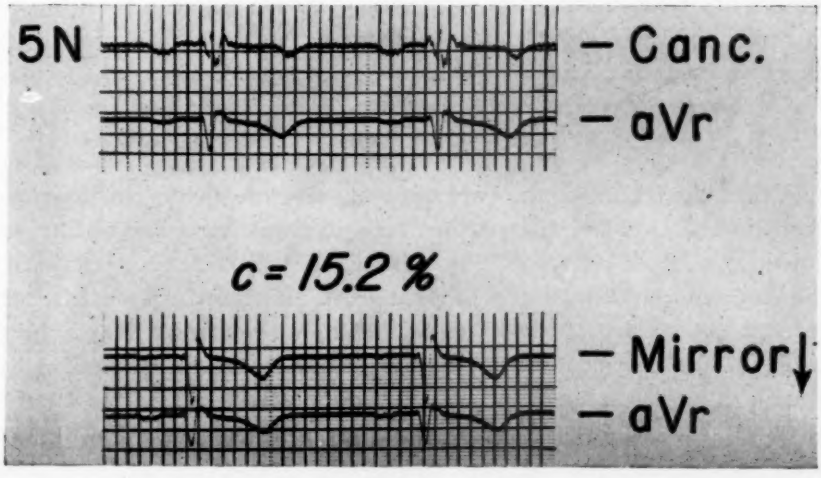

Fig. 6.—An example of poor correspondence between Lead aVR and its best precordial mirror pattern. Although the cancellation coefficient is "fair," there are patent differences between the two QRS complexes, especially in the final 0.04-second period. During this period the precordial tracing exhibits sizable potentials, probably due to local influences, which have relatively little counterpart in Lead aVR. This example also shows how quantitation of cancellation data on the basis of peak-to-peak amplitudes may produce deceptively favorable results by lumping badly matched with well-matched results.

electrocardiograms. Seiden and Keisman contend that, although a pattern which is diagnostic of a particular abnormality may appear "in anatomic proximity to the site of the myocardial disorder, some position remote from the injured area must similarly reflect these abnormal dipole components."

This conclusion appears to be supported by some of their published illustrations even though there are obvious differences between the precordial patterns and their images. But in their example of complete left bundle branch block the mirror pattern contains an initial positive deflection which has no counterpart in the corresponding precordial lead. If there were such a precordial counterpart, it would appear as a small Q wave, which characteristically does not occur in complete left bundle branch block.[20]

For the various reasons which we have outlined we believe that electrocardiographic cancellation is a shaky foundation upon which to establish the validity of the equivalent cardiac dipole concept. Upon initial consideration cancellation appears to provide a highly sensitive null type of technique similar to those upon which various types of precise electrical measurements are based. But further considerations, particularly those related to the lead-field concept of cancellation, to the cancellability of two dipoles, and to errors due to the lumping of good data with bad in the quantitation of the results, indicate that the technique is actually rather insensitive and somewhat misleading.

Certainly, electrocardiographic cancellation bespeaks simple dipolar behavior of the heart within certain limits. Perhaps these limits are rather narrow in healthy individuals, but they are probably much wider in certain disease states than the published data and associated interpretations indicate. It seems likely that precordial electrocardiograms, particularly in disease, may contain important nondipolar (local influence) components, and that the clinical importance of such components will increase as our ability to recognize and interpret them grows. Accordingly, we feel that the continued registration of multiple precordial leads as a standard clinical procedure is warranted.

SUMMARY

Nondipolar (local influence) components of the electrocardiographic generator were investigated by comparing leads derived from the apical portion of the precordium with Lead aV_R. An advanced type of four-electrode cancellation technique was employed for this purpose. The data were interpreted on the basis of an ancillary study of cancellation in electrocardiographic models, in which deviations from simple dipolar behavior were represented as translocation of the equivalent cardiac dipole during depolarization.

Both studies appeared to confirm predictions based on the null-lead theory of cancellation that (1) the inherent properties of cancellation networks render them relatively insensitive to the electromotive forces of the heart, and (2) there is prior assurance of complete cancellation at numerous pairs of instants during depolarization. The location of the equivalent cardiac dipole is not necessarily identical at each instant of complete cancellation. On the contrary, progressive translocation of the dipole is likely to have occurred between two such instants.

The 2-channel registration technique employed in this study revealed definite electrocardiographic nondipolarities over the apical precordium, the clinical significance of which requires further clarification. Unfortunately, it appears that the cancellation technique, at least in its present form, will provide relatively little detailed information about deviation of cardiac behavior from the simple fixed-location dipolar schema.

The authors are greatly indebted to Dr. Richard McFee, of The L. C. Smith College of Engineering, Syracuse University, for a number of helpful suggestions and constructive criticisms. The development of models containing two equivalent dipoles was suggested to us by Dr. Robert H. Okada and Dr. David B. Geselowitz, of The Moore School of Electrical Engineering, University of Pennsylvania. Invaluable technical assistance was rendered by Erskine Lowe, Jr., and Morris Frazier.

APPENDIX

Some Details of the Double Cancellation Phenomenon.—Fig. 7 illustrates a hypothetical model which was derived from the physical model shown in Fig. 3. The semicircular accession layer, $A = A' + A''$, is replaced by a horizontally oriented, equivalent dipole, D_1, located at the radius center of the accession layer. The segment A″ is replaced by another equivalent dipole, D_2, located at the midchordal point of the segment, and oriented normal to A″. Otherwise, the geometric relations and lead connections are identical in the two models, except that in the hypothetical model the search electrode, S, is free to move about the periphery.

Reciprocally energizing S as a "unipolar" electrode produces a lead-field[18] gradient, $\mathbf{L'}_S$, at D_2. In accordance with lead-field theory,[17] $\mathbf{L'}_S$ is proportional to the lead vector[21] at D_2, owing to the search electrode. For purposes of convenience the proportionality will be treated as unity in this development. $\mathbf{L'}_S$ is directed from D_2 toward S, and its length is inversely proportional to the distance between the two points. As the search electrode moves along the periphery of the model, $\mathbf{L'}_S$ rotates about D_2 with its terminus falling on the dashed circular locus.

$\mathbf{L}_{EE}$ is the lead vector owing to the return terminal (the center tap of a large-valued resistor joining E_1 and E_2). In the illustration the origin of $\mathbf{L}_{EE}$ has been translocated from the origin to the terminus of $\mathbf{L'}_S$. The vector sum of the two, $\mathbf{L}_S$, is the lead vector at D_2, owing to the bipolar search electrode connection. As the search electrode is moved about the periphery of the model, its bipolar lead vector terminates in the solid circular locus shown in Fig. 7. This locus is identical to the dashed circle except that all points have been shifted a distance, $\mathbf{L}_{EE}$. $\mathbf{L}_R$, the lead vector at D_2, owing to the bipolar reference electrode connection, also terminates in the solid circular locus at the particular position shown.

For any position of the search electrode to the right of E_1 and E_2 there exists some potentiometer setting, n, which produces complete cancellation of the horizontally oriented dipole, D_1. Associated with each such combination is a vector, $\mathbf{L}$, which is equal to the vectorial sum

$$(1 - n)\,\mathbf{L}_R + n\mathbf{L}_S$$

This is the lead vector at D_2, owing to the cancellation connection. For all such combinations of search electrode location and potentiometer setting the lead vector, $\mathbf{L}$, was found to terminate in the curved locus, C. Therefore, it is apparent from the figure that it is possible to produce double cancellation not only when D_2 is oriented normal to A″, but also for almost any other orientation.

With D_2 radially oriented the conditions required for double cancellation correspond very closely to those shown in Fig. 3. This observation tends to confirm the validity of representing given accession layers as corresponding equivalent dipoles. Although the search electrode position in Fig. 7 is considerably removed from the location required for double cancellation, the lead vector, $\mathbf{L}$, is within 20 degrees of normal to the originally specified axis of the equivalent dipole, D_2. This means that the particular cancellation connection shown in the figure is relatively insensitive

to D_2, and is thus in accord with the corresponding insensitivity which we observed in the physical model that contained two equivalent dipoles. Taking into account also the fact that the electrical moment of D_2 is only one sixth that of D_1, it is apparent that D_2 produces relatively little potential difference between the cancellation terminals.

Double Cancellation in Homogeneous Laminar Models of Irregular Shape.— Although double cancellations were demonstrated under a wide variety of conditions, some objections might be raised on the grounds that the geometrical properties of the models were quite simple and arbitrary. Such objections can be met on a qualitative but theoretically rigorous basis without the necessity of actually testing various types of irregularly shaped laminar models.

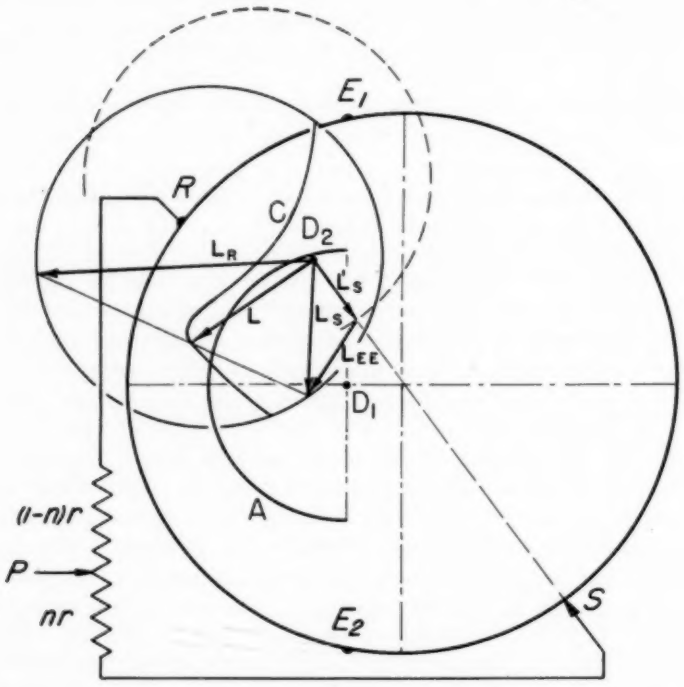

Fig. 7.—A hypothetical circular lamina which illustrates some detailed aspects of factors involved in double cancellation. The electrode positions correspond to those shown in Fig. 3, except that the search electrode (S) is free to move about the periphery of the lamina. The accession layer of Fig. 3 ($A = A' + A''$) is replaced by a horizontally oriented dipole which is centered at D_1. The accession layer A'' of Fig. 3 is replaced by an equivalent dipole which is centered at the midchordal point, D_2, of the layer, and oriented normal to it. For the various network combinations which produce complete cancellation of the dipole at D_1, the lead vector $\mathbf{L}$, which originates at D_2, terminates somewhere along the curved locus C. Consequently, it is possible to produce double cancellation of the horizontally oriented dipole at D_1 together with a dipole of almost any orientation at D_2.

Consider a simple circular model containing two dipoles which are so located and oriented that they are susceptible of double cancellation. Next, subject the model to a Schwarzian transformation[22] which alters its shape in some desired manner. Such a transformation does not alter the isopotential distribution of the two dipole fields relative to each other or relative to the periphery of the model. Consequently, a four-electrode network which produces double cancellation in the circular model will serve the same function when applied to the corresponding peripheral points on the transformed model.

Thus, application of the Schwarzian principle to the results obtained on simple circular models indicates that the double cancellation concept is valid in homogeneous laminas which possess an infinite variety of shapes, equivalent dipole locations and orientations, and peripheral electrode positions.

Double Cancellation in 3-Dimensional Volume Conductors.—As shown in Fig. 7, the electrocardiographic image "surface" relative to a point located within a homogeneous, circular lamina is a circle. In the analogous case of a homogeneous, spherical conductor the image surface proves to be a sphere. With this information in hand, it is apparent that the spherical volume conductor is closely analogous to the circular case, and therefore double cancellation is assured under a wide variety of conditions.

It is also likely that the case of the irregular volume conductor is analogous to the irregularly shaped lamina. If this were so, double cancellation would be a valid concept in the irregular volume conductor also. Although we have no rigorous supporting evidence at this time, our findings on human subjects are quite compatible with the idea.

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Electrocardiographic Evaluation Studies on Quinidine-Induced Changes of Myocardial Conduction

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The subtle property of quinidine that can convert atrial fibrillation to sinus rhythm has eluded all investigators. Therefore, it appeared desirable to re-evaluate the effects of quinidine on the myocardium, as measured by modern techniques of electrocardiography and vectorcardiography, in an effort to define this property.

At the present time it is customary to attribute the therapeutic effectiveness of quinidine to a prolongation of the refractory period of the heart, and cardiac toxicity to its slowing of myocardial conduction. However, recent studies[1] have cast doubt on the validity of these concepts.

Instead of "slowing of myocardial conduction," Lewis and associates[2] used the term "depression of intraventricular conduction." As a result of this concept it was assumed that depression of conduction could become greater with toxic dosage of quinidine, increasing to the degree that intraventricular block appears and serious arrhythmias develop by a "ventricular escape" mechanism. Hence, the admonition that quinidine therapy for atrial fibrillation must be discontinued if the QRS interval is increased 25 per cent over pretreatment values; the broadening of the QRS interval is assumed to be a measure of the slowing of conduction. Other investigators[3-5] have stated that the prolonged QRS interval is the result of a bundle branch block produced by quinidine. Thus, quinidine's slowing of conduction may be interpreted as acting either on the entire conduction system or at a local site, i.e., at the bundle of His. The paradox remains that although ventricular arrhythmias are believed to be a toxic manifestation of quinidine's slowing of myocardial conduction or block, it is the drug of choice for terminating clinical ventricular tachycardia.[6]

Finally, it should be noted that quinidine-induced changes of the refractory period or myocardial conduction are but electrical correlates of an underlying cellular alteration. A more precise understanding of quinidine's action may be had by connecting these electrical correlates with the significant changes in heart action which result from an alteration of sodium and potassium concentrations.

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METHODS AND MATERIALS

Adult mongrel dogs were anesthetized with 35 mg. per kilogram of sodium pentobarbital, administered intraperitoneally. Quinidine gluconate was injected intravenously at a constant rate of infusion for each experiment.

At least two electrocardiograms were recorded simultaneously, using a four-channel Sanborn Poly-Viso Cardiette; Lead II was recorded in all experiments, and precordial leads were taken from various positions on the right or left chest. For convenience, certain of the leads are labeled V_{3R} or V_6 and indicate right or left heart patterns rather than anatomic location. Femoral artery pressures, and venous pressure using the common iliac vein, were obtained with catheters and isometric strain-gauge manometers. In some experiments, respiratory movements were observed with a strain-gauge tambour connected with a Magill orotracheal tube. In addition, frequent, direct examination of the oral mucous membrane was made to detect signs of cyanosis.

The various time intervals of the electrocardiogram were measured with the aid of fine calipers and a magnifying glass. A paper speed of 50 to 100 mm. per second facilitated this work. The QRS, P-R and Q-T time intervals were measured in the manner of reading a clinical electrocardiogram.

Any change (broadening) of the QRS interval was interpreted as the direct result of quinidine action, for it has been reported[7] that the duration of the QRS complex is not altered by a change in heart rate. Both the Q-T and P-R intervals are known to lengthen with a decrease in heart rate. Thus, $Q\text{-}T_c$ and $P\text{-}R_c$ intervals were calculated to define whether any change recorded during the experiment was the result of drug action or was secondary to an altered heart rate.* Bazette's[8] formula, $Q\text{-}T_c = \frac{Q\text{-}T}{\sqrt{R\text{-}R}}$, was adopted for the Q-T interval, while Fujiwara's[9] relationship between P-R interval and heart rate was converted algebraically to the following expression:

$$P\text{-}R_c = \frac{1.754 P\text{-}R}{R\text{-}R^{0.122}}$$

In accordance with accepted electrocardiographic principles, the QRS time interval and the width of the P wave were interpreted as indicating ventricular and atrial depolarization times. Values for ventricular repolarization time were obtained by subtracting the QRS interval from the Q-T interval. The expression "end of S wave to end of T wave (S_eT)" was adopted as a measure of repolarization time. It was assumed, a priori, that this interval would also vary with heart rate. "Correction" was made by dividing the S_eT by a square root function of the R-R interval, as with the $Q\text{-}T_c$.

It is not possible to obtain a measure of the true atrial repolarization time during sinus rhythm since the T_a wave is submerged in the QRS complex. Values for P_eR_c (comparable to S_eT_c) were calculated in the hope that they would indicate the direction of quinidine's action on atrial repolarization time. Albers and Urban's[10] equation was transformed mathematically to yield:

$$P_eR_c = P_eR - 0.325\,(1 - R\text{-}R)$$

The time required to inscribe the P wave (atrial depolarization) having been subtracted from the usual P-R interval was used for P_eR.

Wave voltages (heights) were measured after adjusting the amplifiers to deliver 1 centimeter of deflection for 1 millivolt.

Plasma electrolyte values were obtained using a Beckman flame spectrophotometer and were compared with known standard potassium or sodium solutions.

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*The $Q\text{-}T_c$ and $P\text{-}R_c$ intervals represent "corrected" values using an arbitrary heart rate of 60 per minute. Formulae for "corrected" intervals are derived from data using normal human subjects and must be interpreted with caution when applied to the dog. Furthermore, such mathematical relationships were established using heart rates varying from 58 to 130 per minute. In the anesthetized dog the heart rates were between 106 and 216 per minute.

RESULTS

Effects of Quinidine on Atrial and Ventricular Depolarization.—The results illustrated in Fig. 1 indicate that the injection of quinidine is accompanied by slowing of the rate of myocardial depolarization; the slowing becomes more prominent with increasing dosage. This action is apparently shared by all portions of the heart. Atrial depolarization, as measured by the width of the P wave, is also retarded by quinidine.

Inspection of the pattern of the QRS complex in right and left precordial leads (Fig. 2) does not suggest that quinidine has provoked a bundle branch block. In the dog, 30 to 35 mg. per kilogram of quinidine produces a 50 per cent, or greater, prolongation of the QRS complex (from control value of 0.04 to 0.06 sec.); this is consistent with the clinical criteria of "complete" bundle branch block. No other indications[11,12] for a localized delay of conduction were observed. Neither a delayed R wave in Lead V_{3R} nor a change in initial direction of QRS forces with depressed S-T segment and asymmetrical inverted T wave in Lead V_6 could be seen after the administration of quinidine. Confirmation of the diffuse nature of quinidine's slowing of myocardial depolarization was obtained by use of vectorcardiograms. The frontal plane QRS-loop vectorcardiogram (Fig. 2), using Wilson's electrode placement, did not show any marked alteration in contour to suggest a right or left bundle branch block. However, some lengthening of the uppermost portion of the counterclockwise inscribed loop is produced by large doses of quinidine.

Effects of Quinidine on Atrial and Ventricular Repolarization.—As is shown in Fig. 3, an increase in the dosage of quinidine was accompanied by a progressive broadening of the Q-T and P-R time intervals (time of total electrical activity). However, most of the apparent prolongation of the Q-T interval is the result of quinidine's slowing the heart rate,* for the "corrected" Q-T_c interval is significantly prolonged only by toxic doses of quinidine. Such is not the case for the P-R interval, because the P-R_c interval is also significantly prolonged by quinidine, despite the removal of the influence of a decrease in heart rate on the P-R interval.

According to current concepts of electrocardiographic theory, the inscription of the T_a and T waves represents the period of repolarization. Since the nature of the isoelectric time period between the end of the QRS wave and onset of T is unknown, many investigators prefer to include it in a measure of "myocardial repolarization time." Accordingly, the interpretation of S_eT (Q-T − QRS = S_eT) and P_eR (P-R − width of P = P_eR) as representing ventricular and atrial repolarization times is subject to question. Arbitrarily, both intervals

*Quinidine administered at the rate of 1.0 mg. per kilogram per minute first caused a transitory increase in heart rate. The increase in heart rate was but 25 per cent greater than the control rate and appeared with low dosage of quinidine, 10 to 15 mg. per kilogram. Thereafter there was a progressive slowing of heart rate as the dose of quinidine accumulated, e.g., at 30 mg. per kilogram the heart rate was 83 per cent of the control rate, and at 80 mg. per kilogram it was but 62 per cent. In human subjects with sinus rhythm the usual dose of quinidine is reported to cause only an increase in heart rate.[13] Similarly, in the conscious dog, Gold and Modell[14] observed only a faster heart rate. When we used a conscious dog for comparison with the experiments wherein anesthesia was used, quinidine in large doses caused bradycardia. Moreover, quinidine caused the same changes in the electrocardiographic intervals in both the conscious and anesthetized dog.

were "corrected" to account for changes due to variation in heart rate. Inspection of the lower curves for S_cT_c or P_cR_c indicate that large doses of quinidine exert a slight and possibly nonsignificant effect on either atrial or ventricular repolarization time periods. In view of errors of the "correction" formulae, we do not interpret a change of P_cR_c, S_cT_c, or $Q\text{-}T_c$ of less than 10 per cent as being significant.

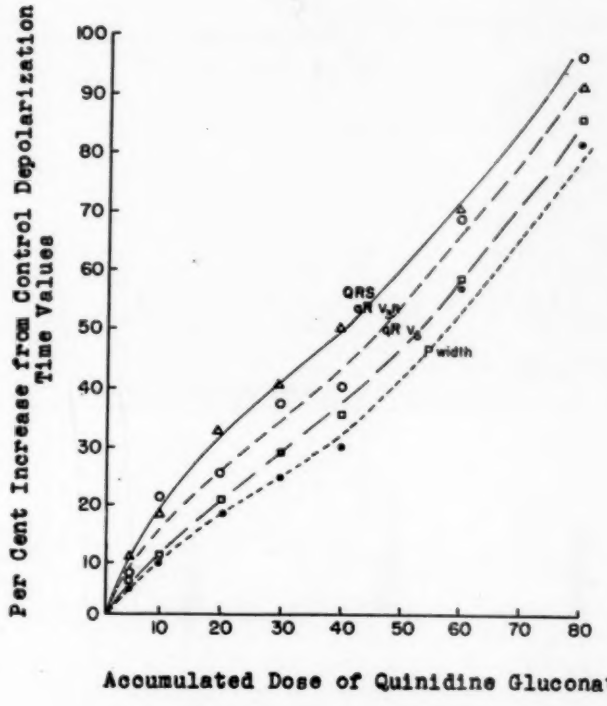

Fig. 1.—Dose-effect relationship between quinidine and slowing of the rate of myocardial depolarization. The width of the P wave is taken as a measure of auricular depolarization; the width of the QRS complex, as ventricular depolarization; and the width of the qR intervals from precordial leads V_{2R} and V_6, as the right and left ventricular activation times. In order to minimize variation, these dose-effect curves are plotted using the percentage change from the control period electrocardiographic time intervals; each point is the mean value obtained from ten dogs.

Factors Affecting the Observed Electrocardiographic Changes Produced by Quinidine: Hypoxia.—It is necessary to rule out the possibility that the electrocardiographic changes previously described are not caused by the direct action of quinidine on the heart. Rather, they may be the result of respiratory or circulatory alterations. These factors can be ruled out in these experiments. The cumulated lethal dosage for quinidine at the various rates of administration was 90 to 135 mg. per kilogram. In the evaluation of the quinidine-induced changes of time intervals of the electrocardiogram an arbitrary upper dosage limit of 60 to 80 mg. per kilogram was selected. With this dosage level there were no arrhythmias, and all waves had their usual configuration.

Death from quinidine occurred primarily from respiratory arrest. The respiratory rate declined with increasing dosage, and its depth was somewhat

lessened. In paired experiments, oxygen was administered through a cuffed Magill orotracheal tube, and respiration was supported by compression of the rebreathing bag. Animals supplied with additional oxygen reflected the same electrocardiographic changes as those observed from quinidine alone; the lethal doses could, however, be increased.

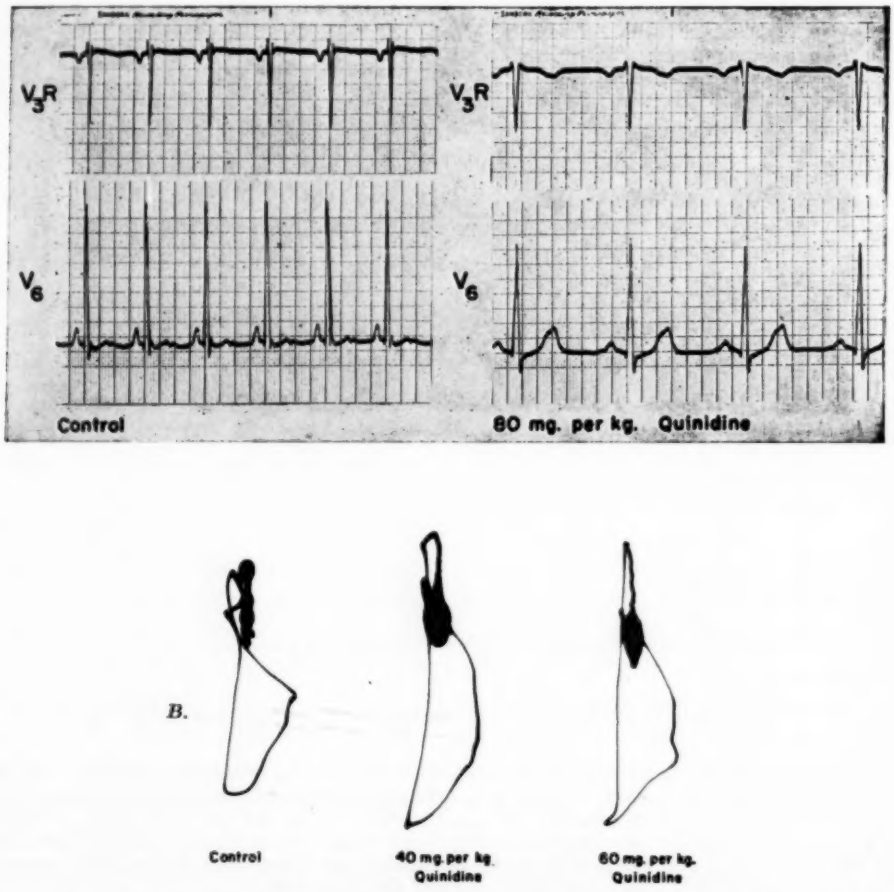

Fig. 2.—*A*, Effect of quinidine on the precordial lead electrocardiograms from the right and left chest. *B*, The corresponding frontal plane vectorcardiograms.

The administration of quinidine is accompanied by a fall in blood pressure which, it is believed, is primarily the result of peripheral vasodilation. Arterial pressures were, however, maintained at 90-100/60 mm. Hg with cumulated doses of quinidine between 25 and 65 mg. per kilogram; even at 80 mg. per kilogram the pressure was at least 60/40 mm. Hg. Nevertheless, it is probable that circulatory and respiratory failure do contribute to the terminal electrocardiographic picture with doses of quinidine of 80 mg. per kilogram and greater.

Electrolyte Changes Accompanying Quinidine.—Certain changes in the electrocardiogram provoked by quinidine are strikingly similar to the altered picture which accompanies variation in plasma electrolytes. Briefly, it is reported

that an increase in the voltage of the T wave correlates with hyperkalemia, while the voltage of the R wave varies inversely with plasma sodium ion.[15]

The administration of quinidine produces an increase in height (voltage) of the T wave,* and an initially inverted wave becomes upright. There is also a diminution in the height of the R wave (see Fig. 2). A striking change was the increase in depth (voltage) of the S wave with increasing dosage of quinidine.

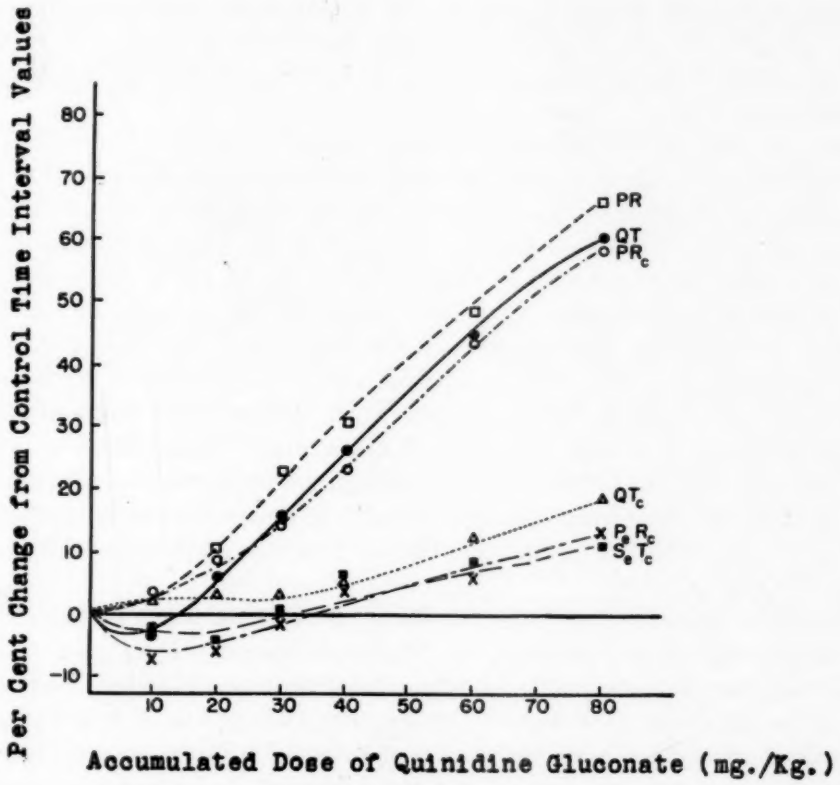

Fig. 3.—Dose-effect relationship between quinidine and certain electrical events of the heart. The Q-T interval represents the total time required for the ventricles to depolarize and repolarize. The P-R interval is a reflection of a similar time interval for the auricles (see text). The end of S to the end of T (S_eT_c) and the end of P to R (P_eR_c) are repolarization times (see text). Corrected time intervals were "adjusted" mathematically to correspond to an arbitrary heart rate of 60 per minute.

Potassium chloride, 2 mEq. per milliliter, was administered to eleven dogs at 0.02 mEq. per kilogram per minute, so that the electrocardiograms could be studied in the same manner as with quinidine. The results are the same as have been reported previously by others.

There was, following potassium administration, a striking increase in T-wave voltage, and there was also an increase in the length of the S wave; these effects paralleled quinidine-induced changes. The administration of potassium, unlike

*In some instances an increase in the height of T was accompanied by narrowing, while in others there was an apparent broadening of the T wave.

that of quinidine, was accompanied by a slight increase in R-wave voltage (by 11 to 17 per cent greater than control values). Another significant difference between quinidine and potassium is that potassium does not cause a prolongation of atrial and ventricular depolarization times. When, however, potassium had accumulated to a dose of 2 mEq. per kilogram, a type of nodal rhythm appeared; the QRS interval was then prolonged, the T wave inverted (Lead II), and the P wave disappeared. The arrhythmias of nearly lethal doses of quinidine and potassium have quite similar contours. At a near lethal dose of quinidine there is some circulatory and respiratory failure, and it is pertinent to recall that Cattell and Civin[16] report a striking increase in serum potassium following brief periods of asphyxia.

That the electrocardiographic changes caused by quinidine are not dependent on an increase in plasma potassium was evident from measurement of electrolytes. When an increase in T and S waves appeared following the administration of 1.25 mEq. per kilogram of potassium chloride, the plasma potassium values were 7 to 9 mEq. per liter. The values rose to 9 to 11 mEq. per liter upon the appearance of nodal rhythm. Quinidine administered to four dogs at the rate of 1.0 mg. per kilogram per minute was not followed by significant alteration in plasma electrolytes. The average control values found were: potassium 3.4, sodium 152, and calcium 10.0 mEq. per liter. When large doses of quinidine had been given, 60 to 80 mg. per kilogram, the average values found were: potassium 4.5 to 4.6, sodium 148 to 150, and calcium 9.0 to 10.0 mEq. per liter. Since the magnitude of these ionic changes is small, it does not appear probable that quinidine's electrocardiographic effects are the consequence of alteration of plasma electrolytes.

Additional experiments were necessary to evaluate the possibility that the effects of quinidine might be related to cellular changes of electrolytes. Quinidine was administered intravenously to dogs, and a portion of the left ventricle was removed for analysis. Samples of the left ventricle removed from other dogs, anesthetized in the same manner but not given quinidine, served as controls. It was found that quinidine, at 60 mg. per kilogram, had caused an average sodium loss of 2.07 mEq. per 100 Gm. of ventricular tissue, and a potassium retention of 2.036 mEq. per 100 Gm. Although this method does not give true values for ionic content of intracellular compartments, these experiments were interpreted as indicating that quinidine causes a cellular retention of potassium and loss of sodium ion.*

Failure of Sodium Lactate to Eliminate Toxicity of Quinidine on the Heart.— Bellet and associates[17] have reported that sodium lactate is beneficial for the "dying heart," and returns to normal the electrocardiographic signs of hyperkalemia. Sodium lactate was administered to seven dogs who had already received large doses of quinidine gluconate. The dosage was 2 to 4 mEq. per kilogram, and the concentration was 0.5 to 1.0 M sodium r-lactate, duplicating the conditions used by Bellet. In dogs given 16 to 60 mg. per kilogram of quini-

*M. M. Gertler reported in an abstract for the American Heart Association, Scientific Sessions, October 25-28, 1957, that quinidine causes a retention of potassium and a loss of sodium in intracellular water of the rabbit myocardium.

dine, sodium lactate caused no change in the electrocardiogram. It was not until 80 mg. per kilogram had been given and the dogs had some degree of hypoxia that some narrowing of the abnormally long QRS, and a slight acceleration of rate, followed the administration of sodium lactate. These latter changes were believed to be a respiratory stimulant effect of the sodium lactate.

DISCUSSION

Our results fail to suggest that quinidine can provoke right or left bundle branch block as has been reported previously in patients and animals.[3-5] It is probable, however, that quinidine's slowing of myocardial conduction will convert a pre-existing (but possibly not recognized) incomplete bundle branch block into a classical complete bundle branch block. Sodi-Pallares[18] suggests that quinidine causes greater slowing of conduction in the subepicardial than in the subendocardial portions of the ventricle. His microelectrode studies lead him to believe that quinidine's "focal" block is somewhere in the locus of the Purkinje muscle fiber. It is possible that the changes seen in the vectorcardiogram, which are probably related to the terminal (S) and possibly also the initial (Q) components of the QRS, represent another measure of this "focal" block.

The slowing of myocardial conduction by quinidine has been accepted traditionally as fostering ventricular arrhythmias which result in sudden death. However, the complete failure of quinidine to provoke ventricular tachycardia or even premature systoles in the dog, coupled with its success in the therapy of clinical ventricular arrhythmias, are serious obstacles to accepting this cardiac toxicity concept for quinidine. Rather, our studies indicate that hypoxia and hypotension produced by quinidine are more invariable causes of cardiac toxicity.

Little correlation can exist between the dosage of quinidine achieved by constant intravenous infusion, as in the experiments reported herein, and that obtained by intermittent oral administration. The continuous infusion of quinidine does yield a progressive series of incremental dosages and an almost infinite series of observations from the continuously recorded electrocardiogram, thus facilitating the interpretation of cause and effect. In using this technique it is assumed that a "toxic parallelism" exists, i.e., effects which are easily measured with toxic levels of a drug also exist, by extrapolation, at therapeutic levels, even though they cannot be detected easily. However, the order of magnitude of prolongation of the QRS complex observed in dogs in this study has been reported in patients with atrial fibrillation receiving quinidine therapy. Therefore, the prolongation of conduction seen in the stage of depolarization may represent quinidine's unique effect, as compared with other myocardially active drugs.

SUMMARY

Quinidine slows the rate of depolarization of both auricle and ventricle, as indicated by a widening of the P wave and the QRS complex; this is an effect which may well be responsible for the drug's effectiveness in atrial fibrillation.

Precordial lead records show no change in contour of the QRS complex following large doses of quinidine; the initial and terminal portions of the QRS complex are equally prolonged. That there is no alteration in the sequence of ventricular depolarization by quinidine is confirmed in that there is neither change of contour nor axis of QRS vector loop. These observations would rule out the production of left or right bundle branch block by quinidine.

Quinidine does not delay atrial or ventricular repolarization. The prolongation of P-R and Q-T intervals by quinidine can be attributed to its reduction of the heart rate.

Lethal doses of quinidine present many of the electrocardiographic features of potassium intoxication at a time when the influence of hypoxia can be ruled out. Although large doses of quinidine do not significantly alter plasma ion concentrations, left ventricular tissue shows the drug to have caused a loss of sodium and a retention of potassium ion; this apparently reflects intracellular changes. Sodium lactate administered to dogs dying from quinidine poisoning exerts a respiratory stimulant action, but cannot restore to normal the quinidine-prolonged QRS complex or width of the P wave.

Nearly lethal doses of quinidine were followed at no time by ventricular tachycardia nor other ventricular arrhythmias, despite considerable prolongation of myocardial depolarization and slowing of heart rate.

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A Correlation Between the Therapeutic Effectiveness of Certain Drugs in Atrial Fibrillation and Their Action on Myocardial Conduction

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It is customary to attribute the therapeutic effectiveness of quinidine to a prolongation of the refractory period of the heart, and its disadvantages to a slowing of myocardial conduction. In terms of the classic circus movement theory, quinidine abolishes fibrillation by narrowing the "excitable gap" as a result of increased myocardial refractoriness. Instances of therapeutic failure are explained by quinidine's slowing of conduction; the "excitable gap" is widened and the circus movement perpetuated. If one prefers to accept the single ectopic focus or multiple ectopic foci theories fo atrial fibrillation, the increased myocardial refractoriness, caused by quinidine, diminishes the heart's response to the postulated ectopic pacemakers.

Van Dongen,[1] in 1936, challenged the importance of a prolongation of the refractory period. He found that certain drugs could prevent electrically induced atrial arrhythmias of experimental animals, although they did not prolong the refractory period; other drugs which did prolong the refractory period were unable to alter the experimental fibrillation. If the refractory period mechanism of action for quinidine were correct, it should apply also to other drugs which have been found effective in clinical atrial fibrillation. Such is not the case. For example, Banthine (methantheline) or atropine prolong the effective refractory period of isolated rabbit atria. With these two drugs, smaller doses than with quinidine are needed to prevent or convert experimentally induced atrial fibrillation of dogs. However, when these drugs are administered to patients, they do not alter the arrhythmias.[2] (Each of the techniques used to provoke fibrillation in dogs is based on a theory of the genesis of atrial fibrillation.)

In the previous report from this laboratory,[3] quinidine was shown to cause a slowing of the rate of auricular and ventricular depolarization. It was found that the P wave and the QRS complexes were broadened; observed changes in P-R and Q-T time intervals did not reflect a slowing of the rate of repolarization, but appeared to be caused by changing heart rate and lengthened depolarization times.

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TABLE I. EFFECTS OF DRUGS USED IN CLINICAL ATRIAL FIBRILLATION UPON THE VARIOUS TIME INTERVALS OF THE ELECTROCARDIOGRAMS OF DOGS

DRUG	NUMBER OF DOGS	RATE OF ADMINISTRATION (MG./KG./MIN.)	CUMULATED MINIMUM LETHAL DOSE (MG./KG.)	CUMULATED DOSAGE AT TIME OF MEASUREMENT	DEPOLARIZATION			REPOLARIZATION	TOTAL ELECTRICAL ACTIVITY	
					ATRIA (P WIDTH)	VENTRICLE (QRS WIDTH)	VENTRICULAR ACTIVATION TIME (qR)	VENTRICLE (S_eT_e)	ATRIA (P-R_e)	VENTRICLE (Q-T_e)
Quinidine gluconate	20	1.0	90	½ MLD ¾ MLD	½ LD +33% ¾ LD_2 +61%	+ 52% + 80%	+ 38% + 72%	+ 3% + 6%	+28% +48%	+ 6% +12%
Allocryptopine hydrochloride[1]	4	1.0	50	½ MLD ¾ MLD	+49% +73%	+ 135% + 182%	+ 33% +133%	0% + 6%	+37% +70%	+ 9% +24%
Pronestyl (procaine amide)	4	5.0	200	½ MLD ¾ MLD	+5.5% +34%	+ 46% + 88%	+7.7% + 33%	+0.7% 0%	+27.9% +50%	+7.4% +11%
Benadryl hydrochloride	10	2.5	57	½ MLD ¾ MLD	+1.1% +0.7%	+10.8% + 38%	0% 0%	+ 3% +6.2%	+12% +16%	+ 3% + 7%
Atabrine hydrochloride[2]	6	0.337	60	½ MLD ¾ MLD	0% 0%	0% 0%	0% 0%	0% 0%	0% − 3%	− 3% + 5%
Banthine bromide	4	0.5	100	½ MLD	0%	0%	0%	+ 12%	+20%	+10.4%

In the present study an attempt was made to correlate drug-induced retardation of atrial and ventricular depolarization with effectiveness in arresting clinical atrial fibrillation.

METHODS AND MATERIALS

The animal experiments were performed on anesthetized dogs, using continuous intravenous infusion of the experimental drug. The continuously recorded electrocardiograms were evaluated in the same manner as has been described in the previous paper.[3]

As is well known, the evaluation of drug therapy in patients is difficult because many variables influence the results. In an attempt to limit errors, the following limitations were placed on the patient data. Therapeutic success was accepted only when electrocardiographic records indicated a conversion of atrial fibrillation to sinus rhythm with an evident P wave. Although some investigators have accepted as an indication of a drug's antifibrillatory potency a slowing of the "f" wave rate, there is no satisfactory evidence that such slowing is always followed by a return to sinus rhythm. Therefore, the reports of the therapeutic trial of the various drugs in patients with atrial fibrillation were included only when the protocols were sufficiently complete to indicate the duration of the arrhythmia.

Sufficient clinical data was available, or was obtained by us, to permit a comparative study of the following drugs: quinidine, allocryptopine (also known as alpha fagarine), Pronestyl (procaine amide), Benadryl (diphenhydramine), Atabrine (quinacrine), and Banthine (methantheline).

The dosage schedule used for quinidine followed the recommendations of Sokolow.[4] Tablets containing 0.2 Gm. of quinidine were administered at 2-hour intervals for five doses. If conversion had not occurred, the dosage was increased each day by increments of 0.2 Gm. until 0.8 Gm. had been reached. Sokolow suggests that the probability of conversion decreases sharply should a dosage greater than 0.8 Gm. every 2 hours for five doses be used. Accordingly, this dosage was accepted as an arbitrary, routine upper limit. Therapeutic failure was not attributed to quinidine if the drug was discontinued because of vomiting or diarrhea before adequate levels had been achieved; patients having such reactions were deleted from the series.

Because of the limited clinical experience with Pronestyl, Benadryl, allocryptopine, Atabrine, and Banthine, maximum dosage schedules have not been established. These drugs, however, were given to patients at a dosage equal to or greater than that required to convert the experimentally induced atrial fibrillation in dogs.

In all patients, digitalis was used whenever congestive heart failure was present or the ventricular rate was increased; such appeared to be the general policy of the other authors whose work is cited.

RESULTS

Effects of Various Drugs on Electrocardiographic Time Intervals in the Dog.— The electrocardiographic changes produced by allocryptopine hydrochloride* have a striking similarity to those of quinidine (see Table I). With the increasing dosage of allocryptopine there is a broadening of the P wave and an increase in the width of the QRS complex. These changes indicate a slowing of the rate of depolarization of atria and ventricles, as was seen with quinidine. Allocryptopine appears not to delay significantly the repolarization of ventricular S_eT_e ($Q\text{-}T_e - QRS$ width), although the $P\text{-}R_e$ interval is prolonged. As with quinidine, after small doses of allocryptopine had accumulated, the height (voltage) of the R and P waves declined, parallelling a slowing of heart rate. In contrast, the

*Obtained through the courtesy of Dr. Gordon A. Alles, Alles Laboratories, Pasadena, Calif.

S and T waves showed a marked gain in magnitude. With allocryptopine there were instances of an exaggeration of wave abnormalities with the appearance of a notched P wave and a notched R′ wave. In some animals electrical alternans was present, with the R voltage varying continuously by 30 to 50 mv. and a 6- to 10-beat cycle.

Benadryl and Pronestyl caused parallel electrocardiographic changes which differed in certain respects from those of quinidine. A slowing of the rate of atrial depolarization by these two drugs required the accumulation of near lethal doses to become evident. Although both drugs cause a broadening of

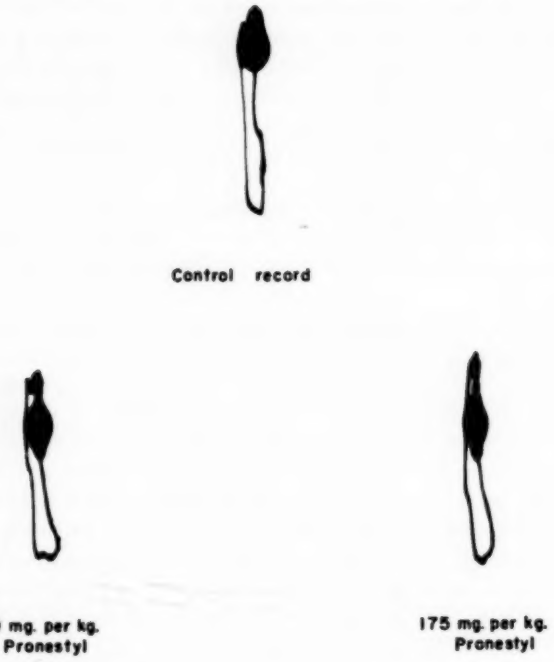

Fig. 1.—Alteration of frontal plane vectorcardiograms, in dogs, with large doses of Pronestyl (procaine amide), using Wilson's suggested placement of the electrodes. The Pronestyl was administered by vein continuously at 5 mg. per kilogram per minute.

the QRS complex, a more significant change occurred in the terminal portion, while the time interval of the intrinsicoid deflection was affected to a lesser degree. This would indicate a greater effect on the near-terminal portions of the ventricular conduction system. Such action was confirmed by the frontal plane vectorcardiogram. As shown in Fig. 1, Pronestyl lengthens the uppermost portion of the QRS vector loop. This is not accompanied by any significant alteration of contour nor direction of the QRSsÊ. A similar action for Pronestyl was described by Sodi-Pallares, who found, from microelectrode studies, a greater retardation of conduction at the epicardial surface than at the endocardial portions of the heart. He describes this action for Pronestyl as a "focal block."[15] With doses of Pronestyl above 100 mg. per kilogram there appeared a slurring of Rs in Lead V_6, the slur appearing near the peak; with increasing doses the slur progressed to the nadir of the S wave. Simultaneously, a similar change

was noted in Lead V_{3R}: a late R′ appeared. This would suggest that the focal block has many of the aspects of a simultaneously produced left and right bundle branch block.

As does quinidine, Pronestyl and Benadryl cause less striking changes in repolarization times, S_eT_e, or time of total electrical activity, $P\text{-}R_e$ and $Q\text{-}T_e$.

Progressively increasing dosage of Banthine or Atabrine was not followed by striking or consistent changes in the electrocardiogram. There was no increase in the width of the P wave nor of the QRS complex; thus, these two drugs did not affect the rate of myocardial depolarization, nor was there remarkable change in the P-R or Q-T time intervals, indicating an absence of action on repolarization.

Death from all drugs was the result primarily of respiratory failure. With both Atabrine and Benadryl, muscular twitching and convulsions occurred which could be controlled by supplementary pentobarbital anesthesia.

All drugs, with the exception of Atabrine, caused a slowing of the heart rate with large dosages. Neither Atabrine nor Banthine resulted in significant changes in voltage of electrocardiographic waves. In particular, there was no reversal of an initially inverted T wave and the increase in height that is seen even after small doses of quinidine or allocryptopine. Changes in wave voltage were similar in direction to, but of lesser magnitude than, those of quinidine or allocryptopine when Pronestyl or Benadryl were administered.

Clinical Trial.—The therapeutic effectiveness of various drugs in patients with "recent" or "chronic" atrial fibrillation is presented in Table II. Only allocryptopine and quinidine caused a return of sinus rhythm in those patients whose fibrillation had been persistent for more than 2 months. Atabrine, Benadryl, and Pronestyl are only effective in patients with fibrillation of recent onset, and seldom convert chronic atrial fibrillation to sinus rhythm. It may be suggested that the occasionally successful conversions of chronic fibrillation which occurred with Benadryl and Pronestyl indicate that the arbitrary 60-day dividing point between "recent" and "chronic" atrial fibrillation was in error. Finally, Banthine in nearly maximum tolerated dosage did not alter the fibrillation of patients whose arrhythmia either was of recent onset or was established (chronic).

TABLE II. THERAPEUTIC EFFECTIVENESS OF VARIOUS DRUGS FOR "RECENT-ONSET" AND "CHRONIC" ATRIAL FIBRILLATION

DRUG	INCIDENCE OF CONVERSION TO SINUS RHYTHM (Number converted/Total patients)				REFERENCES
	RECENT ONSET (Less than 30 days)		CHRONIC (2 mo. to 7 yr.)		
Quinidine	19/20	95%	16/20	80%	——
Allocryptopine	1/1	100%	5/6	83%	5–6.
Pronestyl	18/22	82%	4/27	15%	11–14.
Benadryl	9/10	90%	2/7	28%	2.
Atabrine	18/34	53%	0/13	0%	7–10.
Banthine	0/3	0%	0/8	0%	2.

DISCUSSION

Our results would suggest that clinical atrial fibrillation may be differentiated into three types. Such a classification will be helpful in the evaluation of drug action. The first or "transitory" type of atrial fibrillation has been produced in human subjects by the injection of acetylcholine.[16-17] It is probable that the atrial fibrillation which is occasionally reported to occur during anesthesia, hypothermia, or in patients with "normal" hearts and an unstable autonomic nervous system is of this type. It also appears likely that the various methods of provoking atrial fibrillation in dogs involve this cholinergic mechanism, for either Atropine or Banthine prevents or terminates the arrhythmia. A second type of clinical atrial fibrillation may be described as paroxysmal, or continuous but of recent origin. Patients with this type of atrial fibrillation respond to Pronestyl, Benadryl, or Atabrine, as described in this paper, as well as to many other chemical compounds. The third type, "chronic or sustained" atrial fibrillation requires vigorous therapy with quinidine or allocryptopine, and its resistance to drugs suggests the influence of an, as yet, unknown maintaining factor; cholinergic stimulation may have been the initiating cause.

Further experiments are necessary to establish the validity of a prolongation of atrial depolarization as a "screening" technique for the invention of new drugs for treatment of clinically chronic atrial fibrillation. Such experiments are in progress.

The results of the correlation of effectiveness of various drugs used in clinical atrial fibrillation with the electrocardiographic changes observed for the same drugs on the normal dog's heart encourages the proposal of a new mechanism of action. The hypothesis states that quinidine and other drugs successful in restoring atrial fibrillation may do so by slowing the rate of atrial depolarization. In acting thus, the retarded depolarization, which is related to atrial conduction, so interferes with chaotic nonsyncytial atrial stimulation and contraction that the control returns to the sinoauricular node. It may be proposed also that the slowing of myocardial depolarization is a reflection of a retardation in the rate of transmembrane cellular exchange of sodium and potassium, but does not alter the equilibrium (i.e., no change in tissue concentrations). Although quinidine's action is not reflected by significant alteration of plasma electrolytes, changes at the cellular level still may occur.

SUMMARY

On the basis of the therapeutic effectiveness of various drugs given trial for the arrhythmia, clinical atrial fibrillation should be divided into three classifications. Transitory atrial fibrillation responds to the anticholinergic drugs atropine or Banthine and is apparently vagal in origin. Continuous atrial fibrillation of recent onset, or paroxysmal in nature, can be terminated by Atabrine, Benadryl, or Pronestyl. Sustained or chronic atrial fibrillation can be converted successfully only by quindine or allocryptopine.

Through electrocardiographic studies on dogs, it was found that only allocryptopine and quinidine retard the rate of atrial and ventricular depolarization.

It is thus proposed that a prolongation of myocardial depolarization is the basis of action of drugs in chronic atrial fibrillation, rather than a prolongation of refractoriness as was assumed previously.

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Severe Orthostatic Hypotension: Case Report and Description of Response to Sympatheticomimetic Drugs

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INTRODUCTION

Severe orthostatic hypotension is an uncommon condition in which a marked fall in blood pressure occurs when the patient stands. In many of the cases previously described, evidence has been adduced indicating that this condition is due to a deficiency in sympathetic nervous reflex activity. In some patients the defect in the autonomic nervous system is associated with some lesion affecting also the somatic component, or there is an underlying disease; in other patients it is apparently a primary disorder. Discussion has occurred as to the site of the lesion, particularly in the primary cases; some workers have postulated that it is "central," others that it is "peripheral." In a recent paper, Barnett, Hamilton and Kay[1] described four new cases and showed that in three of these the lesion was "peripheral" (in efferent sympathetic nervous pathways) and in the fourth "central" (in the neuraxis, above the origin of preganglionic sympathetic nerves), thus demonstrating that it may occur in both sites.

In this paper we report another instance of primary orthostatic hypotension, with certain remarkable features not previously noted, and describe responses to various sympatheticomimetic drugs in this patient and in another case reported in the earlier paper.[1]

CLINICAL HISTORY

A.S., a 28-year-old petty officer, had enjoyed good health until 5 weeks prior to admission to the Alfred Hospital, Melbourne. His illness began with lower abdominal pain, diarrhea, difficult and painful micturition, and a sensation of heat and flushing of his hands and feet, followed in a few days by tinnitus when standing, and blurred near-vision. On about the fourteenth day of his illness he was admitted to a Royal Australian Navy hospital. At this stage it was noted that his blood pressure was 135/90 mm. Hg, and both pupils were dilated, unequal, and did not react to light. His abdomen was slightly distended and very resonant to percussion. About the seventeenth day of his illness he developed several attacks of severe dimness of vision when in the erect posture, and it was noted that his blood pressure, when lying, was 100/60 mm. Hg.

About 3 weeks after the onset of his illness he was transferred to a Repatriation Hospital, where he had several episodes of loss of consciousness when erect, with complete and rapid re-

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covery upon lying down. One attack was associated with an epileptiform seizure in which he was incontinent of urine. When lying, his systolic blood pressure was 100 to 110 mm. Hg; on standing, it fell rapidly, and when it was below 40 mm. Hg, he experienced faintness and loss of vision. At this stage his diarrhea was less severe and his urinary disturbance had subsided. Enquiry elicited the fact that he had been virtually impotent for six weeks and that he had lost 28 pounds in weight during his illness. Lumbar puncture revealed cerebrospinal fluid under normal pressure, with a normal response to the Queckenstedt test.

Five weeks after the onset of his illness he was transferred to the Alfred Hospital. He was then a thin young man with a blood pressure, when lying, of 120/70 mm. Hg and a pulse rate of 64 per minute. Both his pupils were dilated, the right being slightly larger than the left, and did not contract in response to light or convergence. Examination of the heart, lungs, and abdomen revealed no abnormality. Apart from the pupillary changes, there were no abnormal neurological findings.

During the patient's stay in the Repatriation Hospital, and later in the Alfred Hospital, various laboratory tests were made, with the results shown in Table I.

Progress and Treatment.—Extensive investigations (see later) were performed to discover the extent and site of the lesion of the autonomic nervous system.

The patient was then treated, in turn, with: "head-up bed" (as recommended by MacLean and Allen[2]) for three days; extra sodium chloride (3 to 5 Gm. per day) plus daily injections of

TABLE I. SUMMARY OF LABORATORY INVESTIGATIONS

TEST	RESULT
Blood Examination:	
Hemoglobin concentration	16.5 Gm./100 ml.
W.B.C. Count	7,000/c.mm. (normal distribution)
E.S.R. (Wintrobe)	4 mm. in 1 hour
Serum Chemistry:	
Sodium	140 mEq./L.
Potassium	4.3 mEq./L.
Chloride	99 mEq./L.
Bicarbonate	28 mEq./L.
Protein	15 mEq./L.
Blood Urea	30 mg./100 ml.
Blood W.R.	Negative
Kline Test	Negative
Cerebrospinal Fluid:	
Protein	50 mg./100 ml.
W.R.	Negative
Cells	16 R.B.C./100 ml.
Electroencephalogram	(1) Diagnostic of epilepsy (examination at Repatriation Hospital) (2) No focal abnormality or evidence of epilepsy (examination 12 days later at Alfred Hospital)
Electrocardiogram	Normal
Feces	Semifluid stool. No blood or mucus. No pathogens
X-ray Examination:	
Chest	No abnormality
Skull	Convolutional markings rather prominent, otherwise no abnormality

DOCA (5 mg. per day) in watery solution for 14 days; and then extra sodium chloride (5 Gm. per day) plus daily injections of DOCA (5 mg. per day) in oily solution. No improvement occurred until commencement of injections of DOCA in oily solution, following which he could stand still without faintness for 5 minutes. Also, he gained weight and felt better. Because of the difficulty in giving daily injections out of hospital, the patient has since been given an intramuscular injection of 75 mg. of microcrystalline DOCA ("Percorten crystules", Ciba) at intervals of 4 weeks. He was also fitted with elastic stockings and an abdominal belt. With this treatment he is greatly improved, although he still has some postural faintness in the mornings, which is relieved by taking one fluid ounce (30 ml.) of Elixir of Neo-Synephrine* (Stearns) each morning.

INVESTIGATION OF AUTONOMIC NERVOUS FUNCTIONS

Sympathetic Nervous System.—

Reflexes: Responses to various tests of sympathetic nervous reflexes are summarized in Table II, and some of the responses are shown graphically in Figs. 1, 2, and 3.

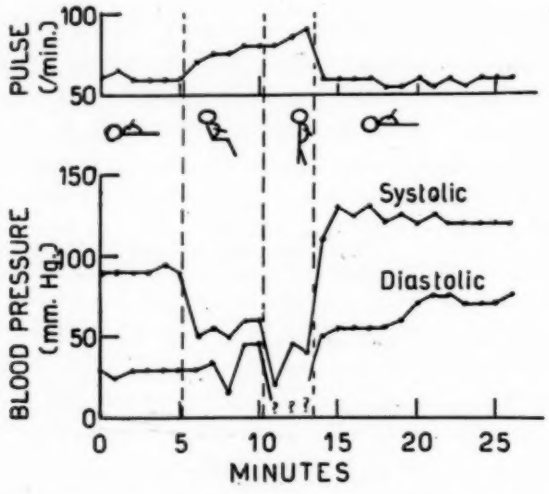


Fig. 1.—Effect of posture on pulse rate and blood pressure in Patient A.S. In this and subsequent figures, the posture is shown diagrammatically by the stick figures.

The tests show widespread loss of reflex sympathetic nervous activity: dilatation of pupils, cardio-acceleration (probably not completely lost), vasomotor responses, sweating, and pilo-erection. Deficiency of vasomotor reflexes was shown by inability to maintain a normal blood pressure in the face of erect posture, venous trapping, Flack test, reactive hyperemia, exercise, by absence of a normal pressor response to pain and cold, and by lack of vasodilatation following reflex heating. The alleviation by arterial occlusion cuffs applied to the thighs and by immersion of the patient in water showed that pooling of blood in the lower limbs was an important factor in the disturbance.

Site of lesion: Theoretically, a lesion in the sympathetic nervous system could occur in receptors, in afferent pathways, in central connections (above the

*Contains 30 mg. phenylephrine hydrochloride.

level of the preganglionic neurone), in efferent pathways (pre- or postganglionic), in the mechanism concerned in liberation of the neurohormone at the nerve endings, or in the effector cells.

Hyperresponsiveness of effector cells (vascular smooth muscle) was demonstrated by a marked rise in blood pressure following a very small dose of l-noradrenalin (Fig. 3). The heart rate also rose, whereas in a normal person it falls.[3]

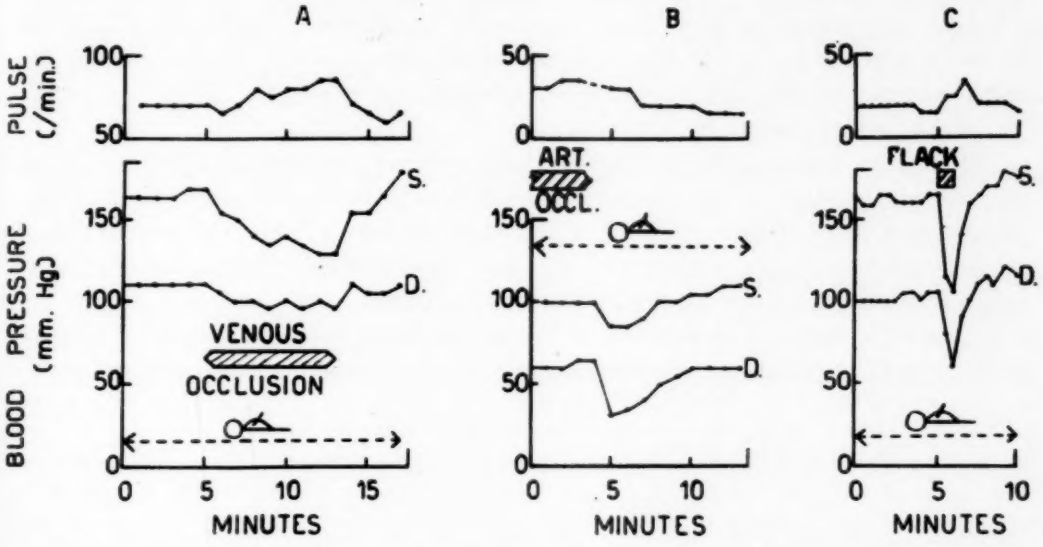


Fig. 2.—Effect of various procedures affecting homeostasis of blood pressure. *A*, Venous trapping. *B*, Reactive hyperemia. *C*, Flack test. During the periods marked *Venous Occlusion* and *Art. Occl.*, venous and arterial occlusion cuffs, respectively, were applied to the upper parts of both thighs. During the period marked *Flack*, the patient maintained a column of mercury at 30 mm. by forced expiration.

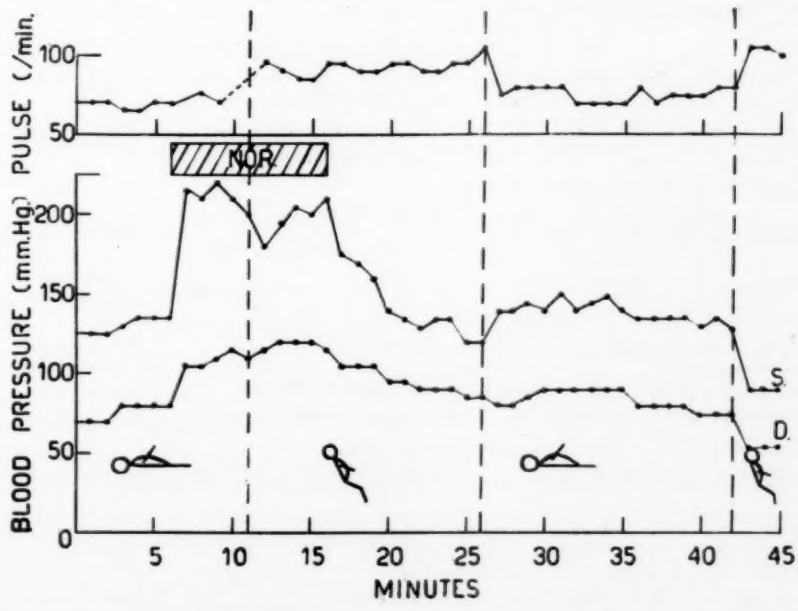


Fig. 3.—Effect of an intravenous infusion of l-noradrenalin at the rate of 3.2 μg per minute on pulse rate and blood pressure in Patient A.S.

Hyperresponsiveness of the dilator pupillae muscle was shown by dilatation of the pupil following instillation into the conjunctival sac of a 1/1,000 solution of Adrenalin, a concentration which produced no effect in a normal person.[4] Lack of function of efferent sympathetic pathways was indicated by the absence of warming of the skin following the anesthetizing of the ulnar and plantar nerves with procaine, and by the absence of pupillary dilatation and flushing of the face following injection of procaine around the left cervical sympathetic trunk. Confirmatory evidence for a lesion in efferent sympathetic pathways was given by the absence of sweating after injection of noradrenalin and pilocarpine locally; the sweat glands atrophy following sympathetic denervation.

Parasympathetic Nervous System.—

Reflexes: Because the parasympathetic reflexes are largely concerned in the activity of viscera, and because testing is difficult, the investigation of this component was incomplete. Results of the various tests (Table III) show loss of parasympathetic reflex activity to the eyes, and possibly some disturbance of reflex salivation, but no certain loss in other regions.

Site of lesion: As in the case of the sympathetic nervous system, the lesion might reside in receptors, afferent pathways, central connections, efferent path-

TABLE II. TESTS OF SYMPATHETIC NERVOUS SYSTEM

OBSERVATION		RESPONSE
A. *Tests Depending on Reflex Sympathetic Nervous Activity*		
Dilatation of pupil from squeezing skin of neck		No response
Effect on blood pressure of:	erect posture	Fall (Fig. 1)
	venous trapping	Fall (Fig. 2,*A*)
	arterial occlusion reactive hyperemia test	Fall (Fig. 2,*B*)
	exercise	No change
	forced expiration (Flack test)	Fall (Fig. 2,*C*)
	pain	Slight fall
	cold	No change or slight fall
Effect on hand blood flow of reflex heating		No change
Effect on heart rate of:	erect posture	Slight rise (Fig. 1)
	exercise	Rise
	pain	Slight rise
	cold	Rise
Sweating from reflex heating		No response
Pilo-erection from cold		No response
Rise in skin temperature after anesthetizing peripheral nerves		No response
Horner's syndrome after anesthetizing cervical sympathetic trunk		No response
B. *Tests Depending on Responsiveness of Organs Supplied by Sympathetic Nervous System*		
Effect on blood pressure of infusion of l-noradrenalin		Marked rise (Fig. 3)
Effect on heart rate of infusion of l-noradrenalin		Rise (Fig. 3)
Dilatation of pupil from instillation of 1/100 Adrenalin		Positive response
Sweating from local injection of l-noradrenalin		No response

ways, or effector cells. Hypersensitivity of the constrictor pupillae, indicating a postganglionic lesion, was shown by pupillary constriction following instillation into the conjunctival sac of 2.5 per cent Mecholyl, a concentration which produces no response in a normal person.[4] It was not practicable to investigate the effect of injection of anesthetic solutions in the region of the parasympathetic nerves.

Effect of Sympatheticomimetic Amines (Table IV and Figs. 4, 5, and 6).— In view of the remarkable pressor response to noradrenalin it was considered of interest to investigate the effect of other sympatheticomimetic amines. An extremely marked pressor response (abolished by intravenous phentolamine) was elicited by phenylephrine and methoxamine, but there was little or no response to ephedrine, Methedrine, mephentermine, and dl-amphetamine. In the doses used, none of the drugs produced a marked rise in blood pressure in the normal subject. Another sympatheticomimetic drug, pholedrine, produced a slight rise in blood pressure of both the patient and a normal person.

Since performing these investigations in Patient A. S., we have had the opportunity of observing the effect of injection of sympatheticomimetic amines in another patient with severe orthostatic hypotension (previously described as Case 2 of Barnett, Hamilton and Kay[1]).

This patient, A.H., at the time of the present investigations was 63 years old, and had suffered from symptoms of severe orthostatic hypotension for 18 years. Previous investigations[1] had indicated a widespread loss of sympathetic functions due to a lesion of efferent pathways. However, sympathetic reflexes were preserved in one arm. There was also evidence for some loss of parasympathetic activity, particularly affecting the carotid sinus reflexes.

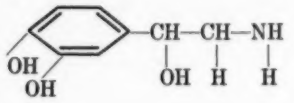
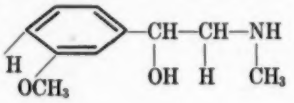
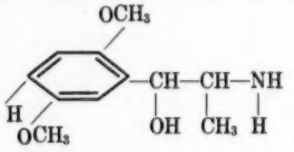
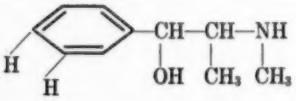
The patient was given injections of phenylephrine and methoxamine, two drugs which had produced a marked rise in blood pressure in Patient A.S., and of ephedrine and pholedrine, two drugs which had had little or no effect in Patient A.S. Because of the patient's age, and the fact that her blood pressure when she was lying down was elevated to approximately 200/100 mm. Hg, smaller doses of methoxamine and pholedrine were given.

As in A.S., phenylephrine produced a marked rise in blood pressure, and methoxamine (in half the dose given to A.S.) produced a moderate rise. However, ephedrine also produced a marked rise in blood pressure, and pholedrine (in half the dose given to A.S.) produced a moderate rise (in contrast to the response in A.S., in whom these drugs had little effect on the blood pressure).

TABLE III. TESTS OF PARASYMPATHETIC NERVOUS SYSTEM

OBSERVATION		RESPONSE
Pupillary constriction from:	light	No response
	convergence	No response
Accommodation for near-vision		No response
Reflex salivation from application of lemon to tongue		No increase over resting level
Effect on blood pressure of:	carotid sinus pressure	Fall
	eyeball pressure	Fall
Effect on heart of:	carotid sinus pressure	Slight rise
	eyeball pressure	Fall
	injection of atropine	Rise

TABLE IV. SUMMARY OF RESPONSES TO ADMINISTRATION OF SYMPATHETICOMIMETIC AMINES

DRUG	FORMULA	NORMAL PERSON			PATIENT A.S.			PATIENT A.H.		
		DOSE	B.P.	PULSE	DOSE	B.P.	PULSE	DOSE	B.P.	PULSE
l-Noradrenalin		—	—	—	3.2 μg/min.	Marked rise	Moderate rise	*	Marked rise	Moderate rise
Phenylephrine		2.5 mg. I.M.	Slight rise	Moderate fall	2.5 mg. I.M.	Marked rise	Slight fall	2.5 mg. I.M.	Marked rise	Moderate rise
Methoxamine		10 mg. I.M.	Slight rise	Moderate fall	10 mg. I.M.	Marked rise	Slight fall	5 mg. I.M.	Moderate rise	No change
Ephedrine		60 mg. I.M.	Slight rise	Slight rise	60 mg. I.M.	No change	Moderate rise	60 mg. I.M.	Marked rise	Marked rise

Methedrine		30 mg. I.M.	Slight rise	Slight rise	30 mg. I.M.	Slight rise	Slight rise	—	—	—
Mephentermine		20 mg. I.M.	No change	No change	20 mg. I.M.	No change	No change	—	—	—
dl-Amphetamine		10 mg.	No change	No change	10 mg. I.M.	No change	No change	—	—	—
Pholedrine		20 mg. I.M.	Slight rise	No change	34 mg. I.M.	Slight rise	No change	10 mg. I.M.	Moderate rise	Slight rise

*The dose of noradrenalin used in this patient was not recorded. The response noted occurred from the local injection of a small amount of a 1/1,000 solution of noradrenalin into the skin at four points, in order to test the response of the sweat glands. (This dose does not cause a significant effect on the blood pressure and pulse rate of a normal person.)

DISCUSSION

Clinical Aspects.—A study of the literature reveals that cases of orthostatic hypotension can be divided into a sympatheticotonic group, in which the sympathetic reflexes are maintained and the postural hypotension is due to excess pooling of blood, and an asympatheticotonic group, in which the sympathetic reflexes are impaired.[5] The features of widespread loss of sympathetic reflex activity noted in Patient A.S. described in this paper clearly indicate that he

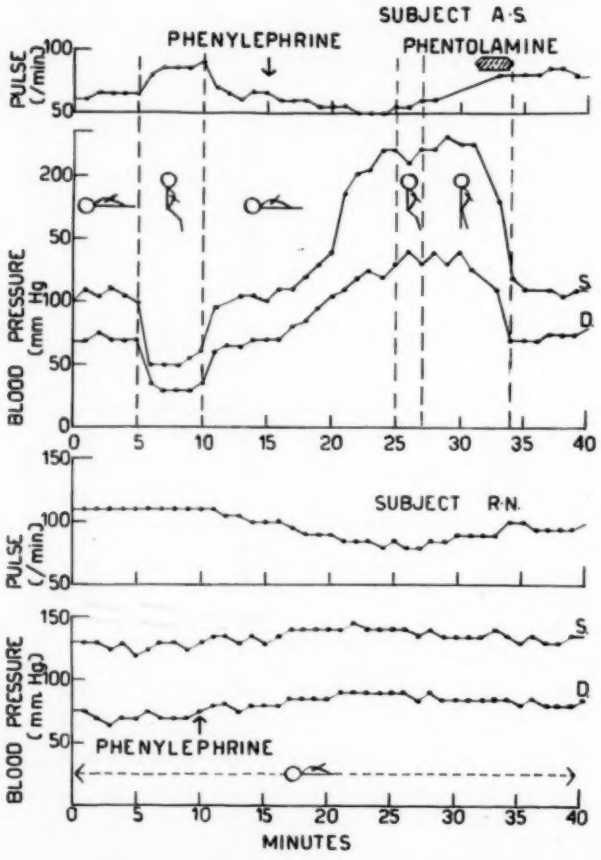


Fig. 4.—Effect of injection of Neo-Synephrine on pulse rate and blood pressure in Patient A.S. and in a normal person, R.N. Intramuscular injections of 2.5 mg. of Neo-Synephrine hydrochloride were given at the points marked by the arrows, and an intravenous injection of 2.5 mg. of phentolamine was given over the period indicated.

belongs to the asympatheticotonic group. In a previous paper[1] it has been shown that the lesion in the nervous system may be either "central" (in the neuraxis above the level of the preganglionic neurone) or "peripheral" (in efferent pathways either pre- or postganglionic). The complete absence of vasodilatation from infiltrating efferent sympathetic pathways indicates that no impulses are passing along them, and that the lesion is situated in these pathways (that is, peripherally). A "central" lesion, although removing sympathetic nervous activity dependent on centers in the neuraxis above the level of the preganglionic neurones,

would not remove sympathetic nervous activity dependent on a spinal reflex arc. The hypersensitivity to noradrenalin also indicates a peripheral lesion, being an example of Cannon's law of the hypersensitivity of a denervated organ to the neurotransmitter. The parasympathetic nervous system is affected to a less extent. The excessive response to local instillation of Mecholyl into the conjunctival sac indicates that here also the lesion is peripheral.

The nature of the underlying lesion remains obscure. Cases of asympathetic-tonic orthostatic hypotension may be either secondary to some neurological disorder (for example, due to trauma, diabetes, syphilis) or apparently primary.

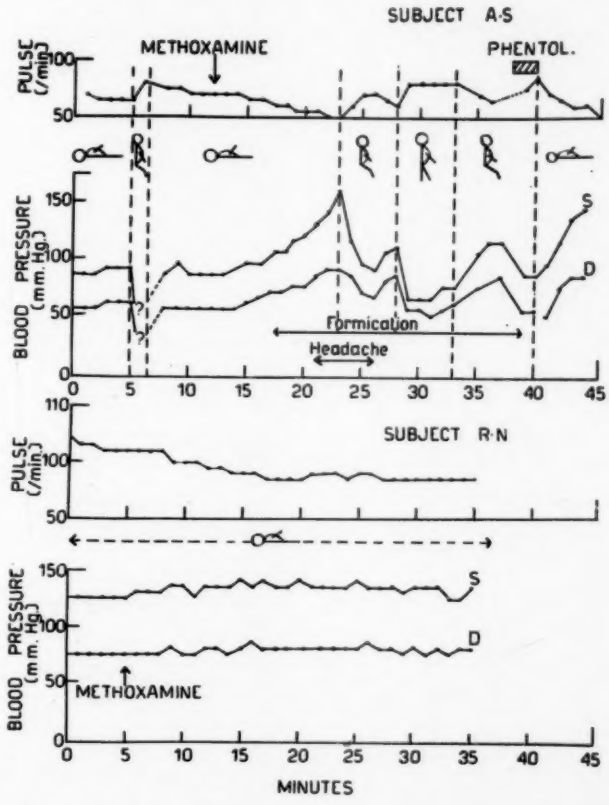


Fig. 5.—Effect of injection of methoxamine on the pulse rate and blood pressure in Patient A.S. and in a normal person, R.N. Intramuscular injections of 10 mg. of methoxamine hydrochloride were given at the points marked by the arrows, and an intravenous injection of 2.5 mg. of phentolamine was given over the period indicated.

In our patient there is no evidence (except for electroencephalographic findings on one occasion) of any neurological disease apart from the dysfunction of the autonomic nervous system. On the other hand, the findings do not conform to the pattern of the primary cases previously described. In the latter the clinical features are, in general, similar to those described by Bradbury and Eggleston[6]: the patients have been of middle age or beyond, and the onset has been insidious over a number of years. We know of no other case similar to the one we describe here in which the onset occurred suddenly with an acute illness and in a young man.

Response to Sympatheticomimetic Amines.—One of the most striking features in A.S is his dramatic response to certain sympatheticomimetic amines, and not to others. Capaccio and Donald[7] obtained results similar to ours, in that there was benefit from phenylephrine and none from ephedrine or amphetamine. On the other hand, Ghrist and Brown[8] and Korns and Randall[9] reported benefit from ephedrine, and Korns and Randall,[9] Davis and Shumway-Davis,[10] and Jeffers and associates[11] reported benefit from amphetamine, drugs which had very little effect in A.S. These divergent results may be explained by the fact that orthostatic hypotension is not a single disease, but rather, as already indicated, a clinical feature which may occur in various pathologic states. It may well be that one type of patient will respond to a certain drug whereas another will not.

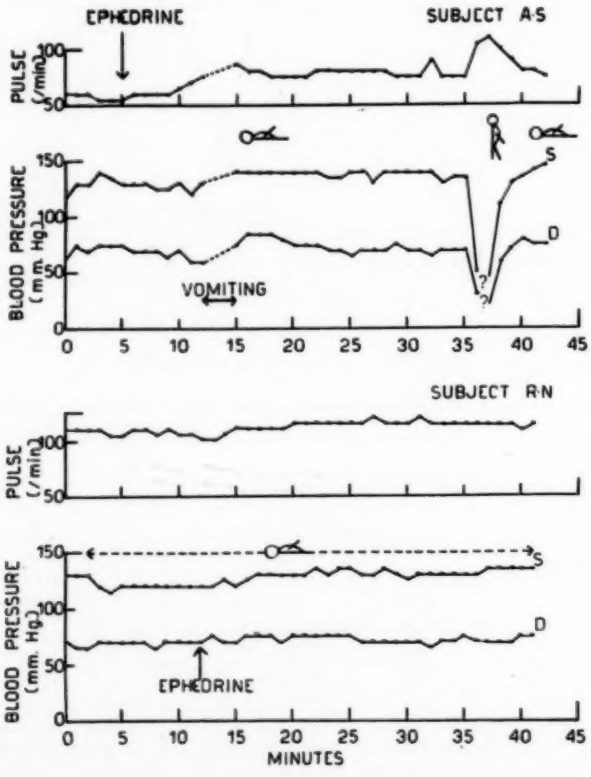


Fig. 6.—Effect of intramuscular injection of 60 mg. of ephedrine hydrochloride on the pulse and blood pressure of Patient A.S. and of a normal person, R.N.

Thus, Barnett and associates[1] found that a case with evidence for a "peripheral" lesion gave a marked response to noradrenalin and little response to ephedrine, whereas a case with evidence for a "central" lesion gave only a moderate response to noradrenalin but obtained more benefit from ephedrine.

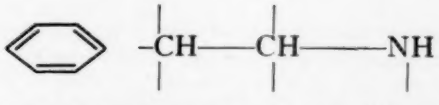
It is of interest to consider the possible explanation of the difference in response between patients to the various sympatheticomimetic amines.

Noradrenalin is believed to act directly on smooth muscle cells,[12] and an excessive response may be due to hypersensitivity of these cells following sympathetic denervation. One view concerning the actions of ephedrine is that at least some of these are explicable by preservation from destruction of a naturally formed adrenergic mediator,[13] and the lack of response to this drug may be due to the virtual absence of naturally formed noradrenalin. The difference between patients with central and peripheral lesions of the sympathetic nervous system in their response to pressor amines could be explained by the hypothesis that these drugs include two groups: one group, including noradrenalin, Neo-Synephrine, and methoxamine, acting directly on cells, and the other group, including ephedrine and Methedrine, acting by preservation of naturally formed noradrenalin. In patients with a "central" lesion the effector cells have normal sensitivity, and some noradrenalin is still being formed through the activity of spinal sympathetic reflexes; a normal response would be expected both to noradrenalin and substances acting directly on cells and to ephedrine and other substances preserving noradrenalin. In patients with a widespread "peripheral" lesion the effector cells are hypersensitive, and practically no noradrenalin is being formed; a supernormal response would be expected to noradrenalin (and substances acting similarly) and a subnormal response to ephedrine (and substances acting similarly).

An apparent paradox is provided by the difference in responses to ephedrine and pholedrine between A.S. and A.H., in both of whom the evidence pointed to a peripheral lesion. A possible explanation is that in A.S. there was virtually complete absence of naturally formed noradrenalin and, in consequence, these drugs were ineffective; in A.H., some noradrenalin was produced in the limb with surviving sympathetic nervous reflexes, and, when preserved, acted on the vessels of the rest of the body rendered hypersensitive by denervation. The hypothesis may, of course, be an oversimplification of the true state of affairs, because it is possible that some sympatheticomimetic amines may act in more than one way.

The effect of the sympatheticomimetic drugs on heart rate is probably a result of two actions: (1) directly on the pacemaker, producing acceleration, and (2) indirectly through the effect of the blood pressure on the carotid sinus mechanism, producing slowing. The tendency to more cardiac acceleration in A.H. may be explained by the greater deficiency in the activity of her carotid sinus mechanism.

It is of interest to correlate the action of the sympatheticomimetic drugs on the blood pressure with their chemical structure. All the drugs used were congeners of Adrenalin and noradrenalin, which have the basic structure shown below:



Substitution may be affected on either the aromatic nucleus or the side chain, with modification of the pharmacologic activity (Goodman and Gilman[12]). In general, sympatheticomimetic activity is increased by substitution of OH groups

in the aromatic nucleus, and maximal activity occurs with two OH groups, as in Adrenalin and noradrenalin. It is noteworthy that the three drugs with marked pressor activity in A.S. (those presumed to act directly on vessels) possessed an oxygen-containing group attached to the benzene ring in the *meta* position, and those drugs which had little or no pressor activity had no such group in this position.

SUMMARY

1. A case is described of severe orthostatic hypotension of acute onset in a young man.

2. Investigation of the autonomic nervous system showed widespread loss of sympathetic nervous activity and more limited loss of parasympathetic activity. In both instances the evidence pointed to a peripheral lesion.

3. A remarkable feature was the extreme sensitivity to certain sympathetic-omimetic amines (noradrenalin, Neo-Synephrine, and methoxamine) and lack of response to others (ephedrine, Methedrine, mephentermine, amphetamine, and pholedrine).

4. The effect of Neo-Synephrine, methoxamine, ephedrine, and pholedrine were noted in another patient with orthostatic hypotension, again with evidence for a peripheral lesion but in this case sparing one limb. In this patient the blood pressure responded to all these drugs.

5. The response of patients with orthostatic hypotension to pressor amines could be explained on the basis of the hypothesis that some pressor amines act directly on vessels, while others act, at least in part, by preserving noradrenalin. The effect will depend on the sensitivity of the vessels and the amount of noradrenalin available for preservation.

Our thanks are due to Dr. T. E. Lowe, Director of the Baker Medical Research Institute, for helpful advice in the preparation of this paper, and to the technical and nursing staff of the Baker Medical Research Institute and of the Alfred Hospital, for help in performing the various tests. We are grateful to the Medical Officers of the Royal Australian Navy and Repatriation Hospital, Heidelberg, for their generosity in making available the early medical notes on Patient A.S.

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Cardiac Dextroposition: Hypoplasia of the Right Pulmonary Artery With Right Venous Pulmonary Drainage Into the Inferior Vena Cava

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The absence or the hypoplasia of one of the main branches of the pulmonary artery is, at the present time, a quite definite clinical and radiologic syndrome, inasmuch as angiocardiography has permitted a diagnosis during life. Several cases of this syndrome have been reported in the literature in recent years.[1-4] Generally, when a complex malformation does not exist in association with it, the absent or the hypoplastic branch usually is the right one.[5-7] Owing to the difference in the irrigation of the two lungs, the syndrome is accompanied by a hyperfunctional left lung and a hypoplastic right lung, which lead, in the majority of the cases, to a pseudodextrocardia through a cardiac dextroposition.

Moreover, since the first descriptions by Dotter and co-workers[8] and Grishman and colleagues[9] of the radiologic and angiocardiographic pictures of the anomalous drainage of the right pulmonary veins into a venous collector which drains into the inferior vena cava, the pattern of these pictures has permitted its identification by standard radiography. A case with the association of both anomalies (absence of the right pulmonary arterial and right pulmonary venous drainage to the inferior vena cava) was published by Welti,[10] in 1950, although without angiocardiographic verification. Another case with identical characteristics, which was observed by us recently, constitutes the object of this communication.

CASE REPORT

N.P.A., Case 4144.—The patient was a 22-year-old woman, seen in May, 1957. Her family history was noncontributory. She was born on term after normal pregnancy and delivery, with normal development and skin coloring. She had no pathologic history of interest until the age of 10 years, when, on a routine medical examination, a dextrocardia was diagnosed. The patient did not show any symptom referable to her circulatory system, and she was sent to us, by Dr. Felíus Riera, because of her cardiac dystopia. The physical examination showed an asthenic woman, 1.60 M. tall, and weighing 45 kilograms. Her skin and mucous membranes were of normal color. There was no clubbing of the fingers or toes. The thoracic examination revealed a clear bulging of the left hemithorax.

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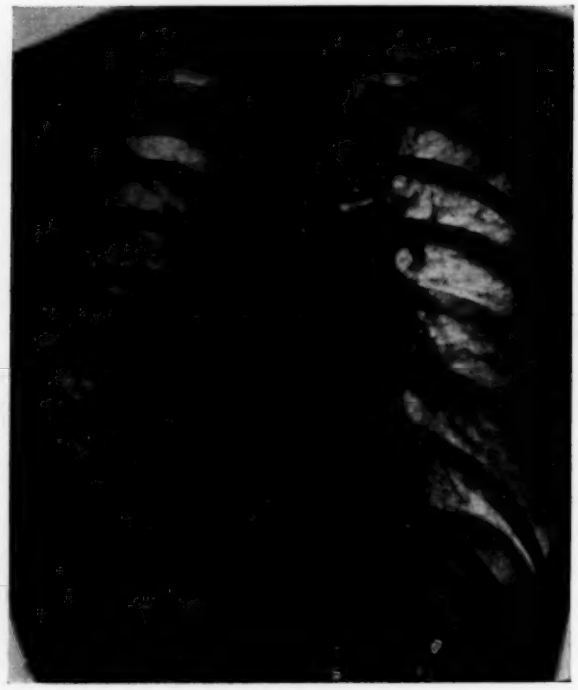


Fig. 1.—Posteroanterior chest radiography showing the features of slight dextrocardia with overdistention of the left lung and increased vascularization. A vascular shadow is clearly seen on the right side, parallel to the right auricular border.

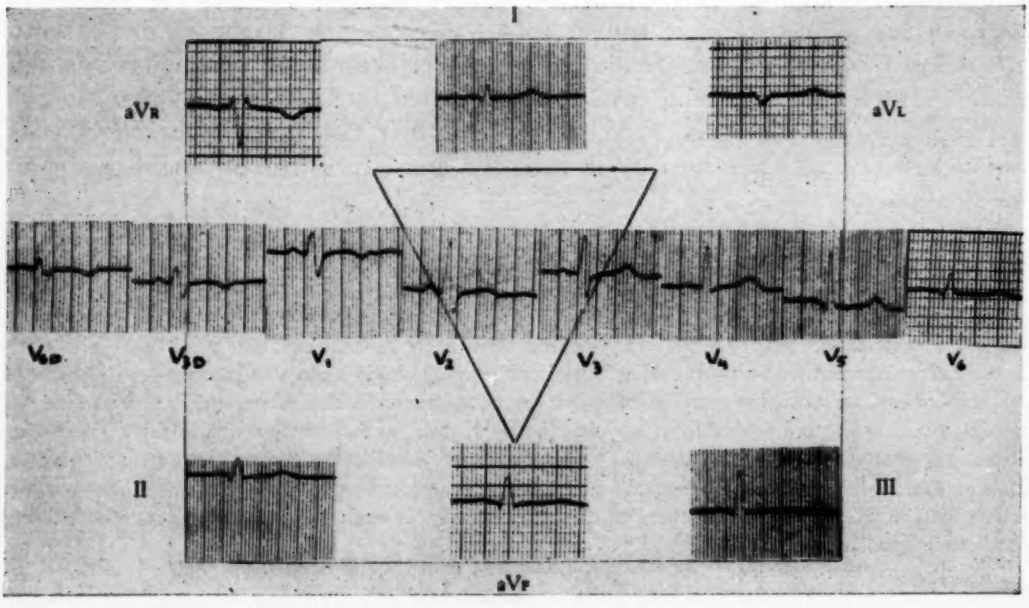
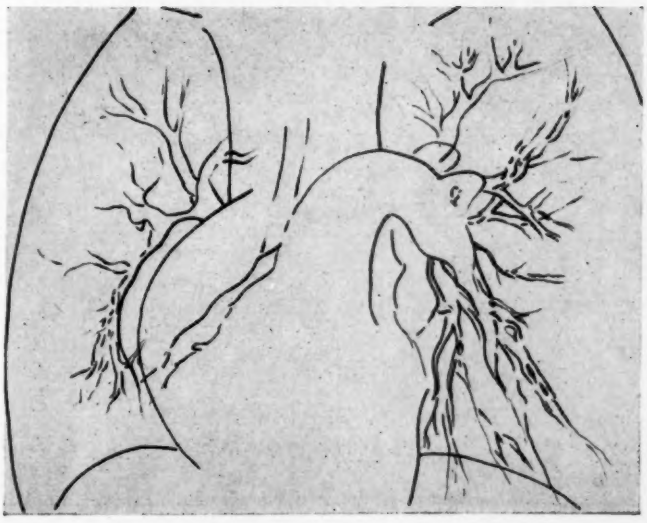


Fig. 2.—Electrocardiogram.

Circulatory System.—The pulse was regular at 80 per minute. The arterial pressure was 110/75 mm. Hg, and with good pulsation in both femoral arteries. The apex beat was felt at the level of the right third intercostal space, 2 cm. from the sternum. Cardiac auscultation revealed the existence of a Grade 3 systolic murmur in the whole right precordial region, with the maximum intensity in the third intercostal space. An ejection systolic "click" preceding the systolic murmur was heard in the region where the pulmonary expansion was felt. A soft diastolic murmur was

A.



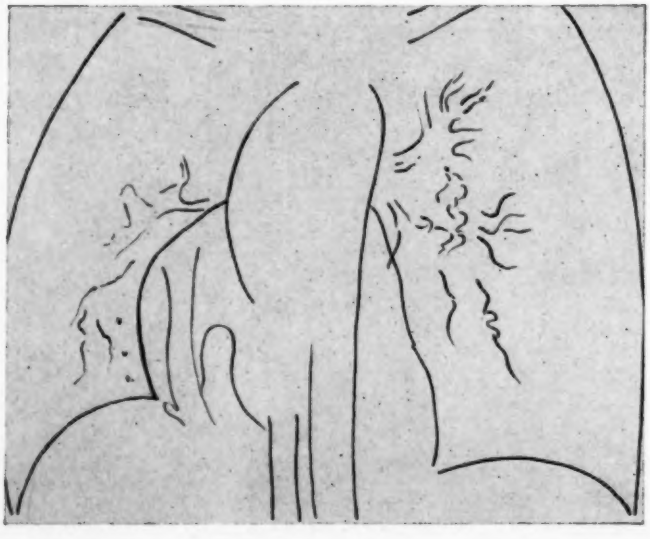
B.

Fig. 3.—*A*, Angiocardiographic exposure showing the filling of the right cavities and the pulmonary artery. Note the increased size of the left pulmonary artery with hypoplasia of the right one. The abnormal shadow is not filled. *B*, Drawing from the angiocardiographic picture of *A*.

also heard in this region. In the whole right posterior lung region of the thorax, especially in the base, a continuous murmur was also heard, with the characteristics of the collateral circulation murmurs.

Radiologic Exploration.—When screening, we were impressed by the overdistention of the left lung, with deviation of the mediastinum to the right, and the abnormal position of the heart, which seemed to be displaced toward the right side (Fig. 1). Observed were a quite evident pulsation in the common pulmonary trunk and a hilar dance in the left pulmonary branch; the

A.



B.

Fig. 4.—*A*, Angiocardiographic exposure showing the filling of the pulmonary venous system and left side of the heart. The abnormal shadow is clearly opacified draining into the inferior vena cava. *B*, Drawing from the angiocardiographic picture of *A*.

latter appeared increased in size. On the contrary, no pulsation appeared in the right branch, the size of which was much reduced. An abnormal shadow appeared parallel to the right inferior cardiac border, suggesting a vascular origin; it began in the hilar region and proceeded toward the cardiophrenic angle. The absence of pulsation in this shadow, as well as its increasing size as it approached the cardiophrenic angle, suggested its venous origin.

The electrocardiogram (Fig. 2) showed a positive P_1 wave, with no axis deviation of the QRS, and a vertical heart. In the extreme right precordial lead, V_6, there appeared a QRS complex of low voltage, with an rSr pattern and an inverted T wave. The other right precordial leads showed an RS pattern with inversion of the RS ratio in Lead V_1 and negative T wave. The electrocardiographic diagnosis was a moderate right ventricular hypertrophy with incomplete pattern of right bundle branch block, and signs of counterclockwise rotation; at the same time, the tracing likewise ruled out the existence of a true dextrocardia.

Angiocardiography.—The angiocardiographic picture showed in the first exposure (Fig. 3) the filling of the right cavities and the pulmonary artery, with evident hypoplasia of the right pulmonary artery; the left one, on the contrary, appeared increased in size, being filled with the bulk of the contrast medium. In the third exposure (Fig. 4) the radiopaque substance was seen in the pulmonary venous system, the left cavities, and the aorta. The right venous pulmonary shadow appeared clearly opacified in this exposure, showing its sinuous way when approaching the cardiophrenic angle and its draining into the inferior vena cava; the latter appeared opacified at the same time.

DISCUSSION

The clinical examination of this patient showed the existence of a pulmonary systolic murmur, with characteristics similar to those of an atrial septal defect, together with a diffused right dorsal continuous murmur, suggestive of collateral circulation. The said clinical data suggested the existence of an associated congenital anomaly. Radiology yielded still more data. The left lung's hyperdistention with the increase of its vascularity, inferred from the unequal size of the two pulmonary branches, with great pulsation in the left branch and the absence of pulsation in the right one, suggested a diagnosis of an atresia or hypoplasia of the right branch of the pulmonary artery; this diagnosis was further corroborated by the existence of the continuous murmur of a collateral circulation in the right side. The anomalous position of the heart was explained by the presence of overdistention of the left lung, owing to a vascular pulmonary anomaly. In fact, the electrocardiography demonstrated that the case had nothing to do with a true dextrocardia, because the P_1 wave was positive. Another important radiologic finding was the existence of a picture of vascular aspect; the vascularity started from the right hilum, parallel to the right auricular border, and proceeded toward the cardiophrenic angle. The absence of pulsations in that picture, as well as its increased size toward its inferior distal part, excluded the possibility of dealing with the right pulmonary branch, and suggested its venous origin. In view of the great similarity of this case to the descriptions by Dotter[8] and Grishman[9] of cases of venous drainage into the inferior vena cava, an angiocardiographic examination was decided upon for the purpose of clarifying said pictures. The angiocardiographic study demonstrated that the left pulmonary branch carried the largest quantity of the pulmonary arterial blood, and showed quite clearly the hypoplasia of the right branch The right paracardiac picture did not opacify within the pulmonary arterial time, but, instead, within the pulmonary venous time, and thus the opacification of

the inferior vena cava took place. The association of this anomaly with an atrial septal defect was observed by Grishman and colleagues,[9] and although the angiocardiographic study of our case did not elicit any finding that might enable its identification, an atrial septal defect cannot be completely excluded in the absence of cardiac catheterization data.

SUMMARY

A case of pseudodextrocardia with hypoplasia of the right pulmonary artery, together with anomalous drainage of the right lung into the inferior vena cava has been described, and the angiocardiographic study reported.

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ADDENDUM

Since the completion of this paper, a similar case has been reported by Wood, Conrad, and Morrow (Am. Heart J. **54**: 422, 1957).

Coronary Arteriovenous Aneurysm: Review of the Literature

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Few reports on pathologic arteriovenous communications between normally distributed coronary arteries and the right side of the heart or coronary veins are available in the literature.

Most arteriovenous coronary aneurysms are undoubtedly congenital anomalies, and only in rare cases are they a sequela of spontaneous rupture of a simple congenital coronary aneurysm.

In embryonic life the coronary arteries communicate with the veins through an ordinary capillary network; but, in addition, the arteries give off branches to the intratrabecular spaces, the sinusoids, which in turn communicate with the cavities of the ventricles. Later, the sinusoids shrink into a normally calibrated capillary network, and the communication with the cavities of the heart is transformed into the thebesian veins.

The anomalies which are considered here may be explained by a preserved fetal communication.[1] Apart from fistulas arising after rupture, only one of the cases on record was of a different origin. The patient in question had an abnormal arteriovenous communication between a normal left coronary artery and the pulmonary artery.[2] It is likely that during its division of the aorta and the pulmonary artery, the spiral septum had cut off a small portion of the cells which should have formed one of the coronary arteries. In this way an accessory coronary artery arising from the pulmonary artery had developed, but owing to the wide communication with the left coronary artery, the shunt was arteriovenous.

From the literature I have collected 14 cases of true arteriovenous coronary aneurysms, including the case reported in this paper (Table I). All these cases have been reported singly, not as part of large autopsied series.

Thus, the present case material does not include cases in which the right (or, in rare cases, the left) coronary artery arises abnormally from the pulmonary artery. In infants this anomaly constitutes a well-defined clinical entity.[3] In the few patients who survive with this anomaly it must be expected that functioning anastomoses exist between the two coronary arteries. However, these anastomoses are difficult to reveal. Thus, in the 4 cases considered by Soloff,[4] they could be demonstrated in only 2.[5,6] Of other arteriovenous shunts which are not included in the present series mention may be made of aneurysms of the sinus of Valsalva which have ruptured into the right atrium. Clinically, the latter may be mistaken for arteriovenous coronary aneurysms, although the

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past history may be helpful in the differential diagnosis (acute episode). Congenital communications between the aortic sinus and the right heart due to defective division of the truncus arteriosus were also excluded. This applies to the case reported by Brown and Burnett,[7] who found a wide communication between the pulmonary sinus and the left aortic sinus in a boy, aged 13 months, in whom the coronary system was normal. The shunt was so pronounced that it had resulted in right-sided atrophy. Auscultation revealed a continuous machinery

TABLE I. CASES OF TRUE ARTERIOVENOUS CORONARY ANEURYSMS REPORTED IN THE LITERATURE

AUTHOR	SUMMARY OF CASE	COURSE
1. Trevor[11] (1911-12)	Girl, aged 11 yr., without known cardiac disease, contracted sepsis. Mitral-like systolic murmur in the tricuspid area. No ECG or roentgenograms available. Right coronary artery dilated with large perforation into the right ventricle	Very pronounced shunt; autopsy finding. Died from sepsis and cardiac failure
2. Halpert[22] (1930)	Man, aged 54 yr., without known cardiac disease. Systolic murmur at the apex. No ECG or roentgenograms available. The right coronary artery anastomosed widely with the coronary sinus. Generalized hypertrophy of the heart	Moderate shunt; autopsy finding. Died of cancer of the stomach
3. Löwenheim[24] (1932)	Woman, aged 62 yr., had for 2 years suffered from cardiac complaints of increasing severity due to hypertension. No information as to murmurs. No ECG or roentgenograms available. Right coronary artery aneurysmal, with small dilated vessel entering the right coronary vein	Moderate shunt; autopsy finding. Died from cardiac failure
4. Harris[25] (1937)	Man, aged 43 yr., without cardiac manifestations. No further information. Right coronary artery aneurysmally dilated, giving off atypical branch into the right atrium	Moderate shunt; autopsy finding. Died from brain tumor
5. Bjørk and Crafoord[2] (1947)	Boy, aged 15 yr., suffered from mild dyspnea on exertion for 2 yr. and had two attacks of pallor, severe dyspnea, and palpitation on exertion. Systolic and diastolic murmur in first left intercostal space. No ECG abnormalities. No definite roentgenographic changes, except hilar dance. Atypical communication between the left coronary artery and pulmonary artery	Pronounced shunt; operative finding. Atypical vessel ligated
6. Emminger[10] (1947)	Woman, aged 43 yr., without cardiac complaints. No information as to auscultatory, ECG, or roentgenographic studies. Right coronary artery aneurysmal, communicated through a fine vessel with dilated great cardiac vein	Slight shunt; autopsy finding. Died from uremia due to chronic glomerulonephritis
7. Paul, Sweet and White[14] (1949)	Boy, aged 9 yr., without serious complaints. Continuous systolic and diastolic murmur audible in the fourth right intercostal space. No ECG abnormalities. Roentgenograms showed a slightly enlarged heart, otherwise normal conditions. Right coronary artery aneurysmal, anastomosed through a vein with the coronary sinus	Moderate shunt; operative finding. No treatment

murmur over the third and fourth intercostal spaces at the left sternal margin; the ECG was normal. This case occupies a position on the border line of arteriovenous coronary aneurysms, since the fact cannot be disregarded that the shunt may have arisen because an accessory left coronary artery has maintained the fetal communication with the right ventricle. The coronary aneurysm observed at operation by Gross[8] was not an arteriovenous aneurysm, but rather a simple intramuscular aneurysm of the same type as that mentioned by Knoblich and Rawson[9]; their patient died at the age of 55 years from cerebral hemorrhage due

TABLE I. CASES OF TRUE ARTERIOVENOUS CORONARY ANEURYSMS REPORTED IN THE LITERATURE—(CONT'D)

AUTHOR	SUMMARY OF CASE	COURSE
8. Essenberg[26] (1950)	22-week-old fetus. Left coronary artery giving off atypical branch entering the right atrium	Slight shunt; autopsy finding. Cause of abortion unknown
9. Williams, et al.[27] (1951)	Girl, aged 4 days, suffering from attacks of cyanosis. No cardiac murmurs. No information as to ECG. Roentgenograms showed cardiac enlargement. Left coronary artery anastomosed with the right ventricle through an atypical vessel and sinusoids; pulmonary atresia	Moderate, possibly veno-arterial, shunt; autopsy finding. Died from cardiac failure
10. Alexander and Green[28] (1952)	Girl, aged 2 days. The dead body was cyanotic; no further information. Left coronary artery entered the right ventricle through an atypical vessel and sinusoids. Hypoplasia of the right ventricle, ventricular septal defect, pulmonary stenosis, and patent ductus arteriosus	Pronounced shunt; autopsy finding. Died from cardiac failure
11. Colbeck and Shaw[19] (1954)	Man, aged 85 yr.; past history that of good health. Signs of arteriosclerotic cardiac disease developed. Systolic and diastolic aortic murmur; systolic mitral murmur. ECG revealed atrial fibrillation and left bundle branch block. Roentgenograms showed enlargement of the heart, especially of the left ventricle. Right coronary artery aneurysmal, giving off an abnormal branch entering the right atrium	Moderate shunt; autopsy finding. Died from acute pulmonary edema
12. Our own case[15] (1955)	Boy, aged 11 yr.; see Case Report (p. 436). Left coronary artery entered the right ventricle through an aneurysmal, abnormal branch	Pronounced shunt; operative finding. Treated with ligation
13. Davis, et al.[16] (1956)	Woman, aged 19 yr., without serious complaints. Continuous murmur in the pulmonary area. No ECG or roentgenographic abnormalities. Heart catheterization showed increased oxygen saturation in the pulmonary conus and pulmonary artery. Left coronary artery aneurysmal, with communication to the right ventricle	Pronounced shunt; operative finding. Treated with ligation
14. Johnson[17] (1956)	Boy, aged 12 mo. No information as to preoperative findings. Abnormal right coronary artery coursed behind the aorta and the superior vena cava to enter the right atrium	Presumably pronounced shunt; operative finding. Treated with ligation

to rupture of a congenital aneurysm of the basilar artery of the brain. In addition, autopsy revealed an aneurysmal descending branch of the left coronary artery, which ended in a pouch, 45 by 45 by 50 mm., in the apical part of the interventricular septum. The pouch was drained by a venous capillary system and was completely cut off from the ventricular cavities. A few years before the patient died, a diagnosis of cardiac disease had been made; roentgenographic examination had revealed enlargement of the heart, and the ECG showed, first, left axis deviation and, later, signs of acute damage of the posterior ventricular wall and the septum. As early as at the age of 18 years, the loud, harsh apical murmur had been disclosed. The 2 cases just mentioned were due probably to a nonobliterated sinusoid. Table II shows the distribution of arteriovenous communications in the 14 cases reviewed in this paper.

TABLE II. DISTRIBUTION OF THE ARTERIOVENOUS COMMUNICATIONS

	RIGHT VENTRICLE	CORONARY SINUS OR CARDIAC VEINS	RIGHT ATRIUM	PULMONARY ARTERY
Coronary artery				
Right	1	4	3	0
Left	4	0	1	1

Of the 14 cases of arteriovenous coronary aneurysms considered here, 5 were diagnosed at operation, while the preoperative diagnosis had been one of patent ductus arteriosus, high ventricular septal defect, or extracardial aneurysm. Four of the patients subjected to operation were treated with ligation of the arteriovenous communication. In the remaining 9 cases the aneurysm was disclosed at autopsy. Three of the cases were complicated by other congenital cardiac anomalies, viz., pulmonary atresia, rudimentary right ventricle with a ventricular septal defect, and patent ductus arteriosus, and by patent ductus arteriosus (our case), respectively.

The sex was not stated in one case, while the remainder were 7 males and 6 females. Their ages ranged from a 22-week fetus to 85 years.

Judging from the reports of the individual cases, 5 patients between the ages of 40 and 85 years had a moderate or slight shunt, while the more pronounced shunts were revealed in patients whose ages ranged from 2 days to 19 years.

It may be presumed that only in 2 cases did the arteriovenous fistula arise as a consequence of rupture of a pre-existing coronary aneurysm. One of these patients was a woman, aged 43, who died from uremia due to chronic glomerulonephritis.[10] A fine communication was found between an aneurysmal right coronary artery and the great cardiac vein. At the entrance of the vein there were two adherent thrombi, which presumably must be interpreted as being sequelae of a rupture, even through the past history was noncontributory. The second case[11] is of greater interest. The patient was an 11-year-old girl who previously had been in good health. She was admitted to hospital because of acute attacks of slight fever, with a sore throat, joint pain, and streptococcemia.

On admission, auscultation revealed extended cardiac dullness to the left, a rough systolic mitral murmur, and a thrill. The murmur was best heard 3 cm. internal to the nipple line. Ten days later, the murmur changed into a to-and-fro cyclic murmur, which was very rough and scratchy, and was best heard over the tricuspid area. The patient died on the fifteenth day in hospital. Autopsy revealed a large perforation from the descending branch of the dilated right coronary artery into the right ventricle. On the ventricular side some thrombi adhered to the perforation, and ulceration of the thin-walled artery was seen around the opening.

Rupture into the pericardium did not occur in any of the known cases of arteriovenous aneurysm or in the cases of true coronary aneurysm of congenital origin considered by Scott.[12] On the other hand, a case of fatal rupture of a congenital coronary aneurysm into the left atrium is on record.[13] The patient was a 34-year-old man who died suddenly after having suffered from embolism for 4 weeks.

All the cases diagnosed during life were disclosed at operation. The first case was reported by Bjørk and Crafoord.[2] In a 15-year-old boy they had made a clinical diagnosis of patent ductus arteriosus. Operation revealed an obliterated ductus arteriosus; the murmur was due to an arteriovenous aneurysm between an atypical branch of the left coronary artery and the pulmonary artery. The aberrant vessel was ligated.

The second case[14] was that of a 9-year-old boy who was subjected to exploratory thoracotomy, because clinical examination had disclosed a continuous murmur in the fourth intercostal space at the right sternal margin, a normal ECG, and, roentgenographically, questionable cardiac enlargement without characteristic changes in the shape. The author had expected to find an aneurysm somewhere in the mediastinum, but the only anomaly was an arteriovenous fistula between the markedly tortuous and dilated right coronary artery and the coronary sinus. Surgical treatment was not attempted.

The third case was our own.[15]

The fourth case[16] was that of 19-year-old woman in whom a continuous murmur in the pulmonary area was observed preoperatively. Heart catheterization showed a higher oxygen saturation in the pulmonary conus of the right ventricle and in the pulmonary artery than at the floor of the right ventricle. It had been expected that operation would reveal a patent ductus arteriosus, but instead it showed dilatation of the left coronary artery, which entered into the conus. A distinct thrill was palpable over the artery, but it disappeared on compression. The artery was ligated after division close to its entrance into the right ventricle. The postoperative course was uneventful.

Only a few details are available of the fifth case,[17] for which reason its nature is rather doubtful. The patient was a boy, aged about 12 months, in whom operation revealed an anomalous right coronary artery that coursed behind the aorta and the superior vena cava to enter the right atrium. The vessel was occluded by multiple suture ligatures. Recovery ensued after a rather stormy postoperative course.

Finally, a case of coronary aneurysm with a communication to the left atrium is on record[18]; the anomaly was disclosed at operation and treated surgically.

The patient was a 10-year-old boy who suffered from mild dyspnea on exertion. A loud continuous murmur with systolic accentuation over the pulmonary area and a faint systolic murmur at the apex were observed. Roentgen examination revealed no definite signs of pathologic changes, nor did heart catheterization show any abnormalities. Operation disclosed that the descending branch of the left coronary artery was aneurysmal, with a vessel entering the left atrium. The murmur disappeared on compression of the fistula, and ligation was performed. The postoperative course was uneventful.

CASE REPORT

Our patient, B.A.I. (5926/54), was an 11-year-old boy who was admitted to Aarhus Kommunehospital for the first time on Nov. 12, 1954. The patient was the second of 5 children; the first and the fourth child had died shortly after birth. The delivery of the patient was normal, but his mother had had German measles during the early months of the pregnancy. The family history did not reveal any cases of cardiac disease.

Blindness of the right eye was observed when the patient was 4 weeks old. Heart disease (murmur) was discovered on a routine examination at the age of 3 or 4 years. The boy had always been small for his age, but was normally nourished. Since he began walking there had been some tendency to dyspnea and fatigue on exertion. Occasionally, a slight cyanotic tinge had been noticed. The mental development was normal.

Physical Examination.—The boy was small and a little slender. There was no cyanosis, and on exertion (400 kilogram-meter/min. for 3 minutes) there was no appreciable dyspnea. Height was 125 cm.; weight was 27.6 kilograms.

Microphthalmia and cataract of the right eye were present. The diameter of the right cornea was 9 mm., as compared with 11 mm. of the left one. With the right eye the patient could dimly see hand movements; the vision of the left eye was fairly good with correction.

Spontaneous undulatory, lateral, and rotatory nystagmus was observed.

The otologic examination revealed considerable perceptive deafness of the left ear, and the hearing of the right ear was not quite normal either. The vestibular function could not be assessed.

Heart examination showed a very slight precordial bulge and a palpable thrill in the apical region. The apex beat was felt in the fourth left intercostal space in the mid-clavicular line. A harsh continuous murmur with a maximum around the second heart sound was heard in the upper precordium, with a maximum intensity of Grade 3 to 4 in the second intercostal space about 2 cm. to the left of the sternal margin. Farther down in the precordium the diastolic component increased considerably and also became harsher, with maximum intensity in the fourth left intercostal space in the parasternal line. The systolic component became fainter in the lower precordium. The second pulmonary sound was accentuated. There was no arrhythmia; the peripheral pulsations were normal. No other abnormalities were observed.

Laboratory Findings.—The blood pressure was 100/75 mm. Hg. Urinalysis showed no protein or abnormal sediment, and no sugar. Hemoglobin level was 93 per cent. Tuberculin test was positive.

Electrocardiography.—The ECG was normal. QRS axis was between +30° and +60°. There was no abnormal splitting or slurring. The T axis was between +60° and +90°. The T wave in Lead I was less than 0.1 mv. The Wilson position was semivertical. P-R interval was 0.15 second, and the QRS 0.07 second. Precordial QRS pattern was normal. There were positive T waves in all precordial leads (Fig. 1).

Roentgen Examination.—The cardiothoracic index was 0.47. Heart volume was 490 ml. = 475 ml./sq.M. of body surface. The heart shadow was normal in the anteroposterior view and left anterior oblique position. In the right anterior oblique position a slight enlargement of the left atrium was noted. Hilar vascular markings and peripheral lung fields were normal. The aortic arch was normal; pulsatory findings were normal.

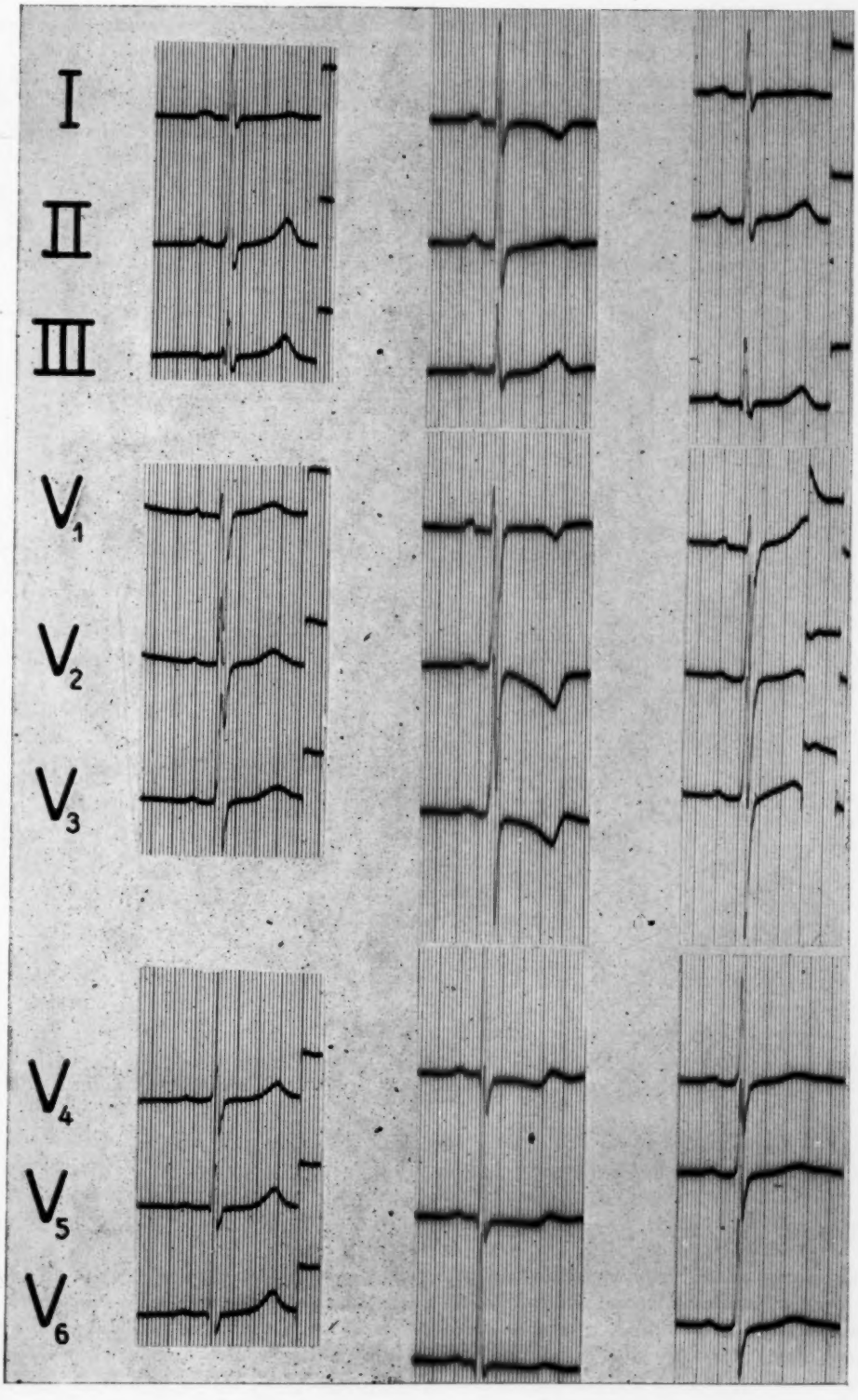


Fig. 1.—Electrocardiograms in our patient (*A*) before, (*B*) 11 days after, and (*C*) 3½ months after the operation.

Physiologic Examination.—At cardiac catheterization the blood samples showed the presence of an arteriovenous shunt in two sites, viz., from the left side toward the pulmonary artery (2.1 L./min.) and from the left side toward the right ventricle (1.6L./min.). It was possible to place the tip of the catheter in the pulmonary artery in a position where a mixed pulmonary artery and aortic pressure curve could be obtained, but this position was nearer to the pulmonary ostium than is usually seen in patent ductus arteriosus, for which reason an aorticopulmonary fistula or unusually short main stem of the pulmonary artery was suspected. The shunt toward the right ventricle suggested the presence of an interventricular septal defect. The right ventricular pressure was found to be slightly elevated, with a small pressure drop to the pulmonary artery, as is often seen in cases of arteriovenous shunt without pulmonary stenosis. The arterial oxygen saturation was normal at rest (van Slyke analysis) and during exercise (oximetry), thus demonstrating the absence of any veno-arterial shunts. Pulmonary function tests showed normal ventilation.

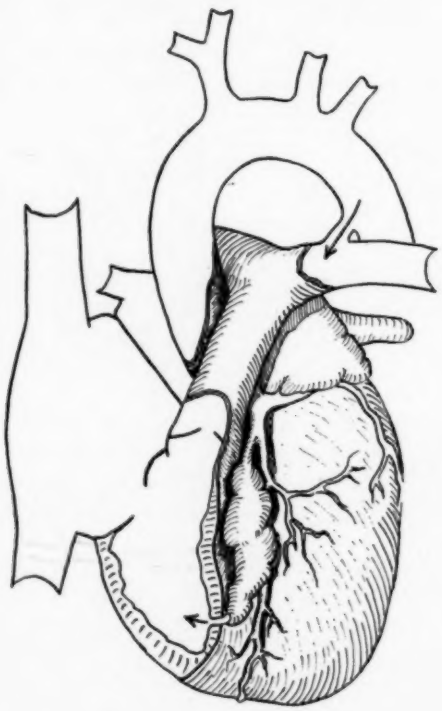
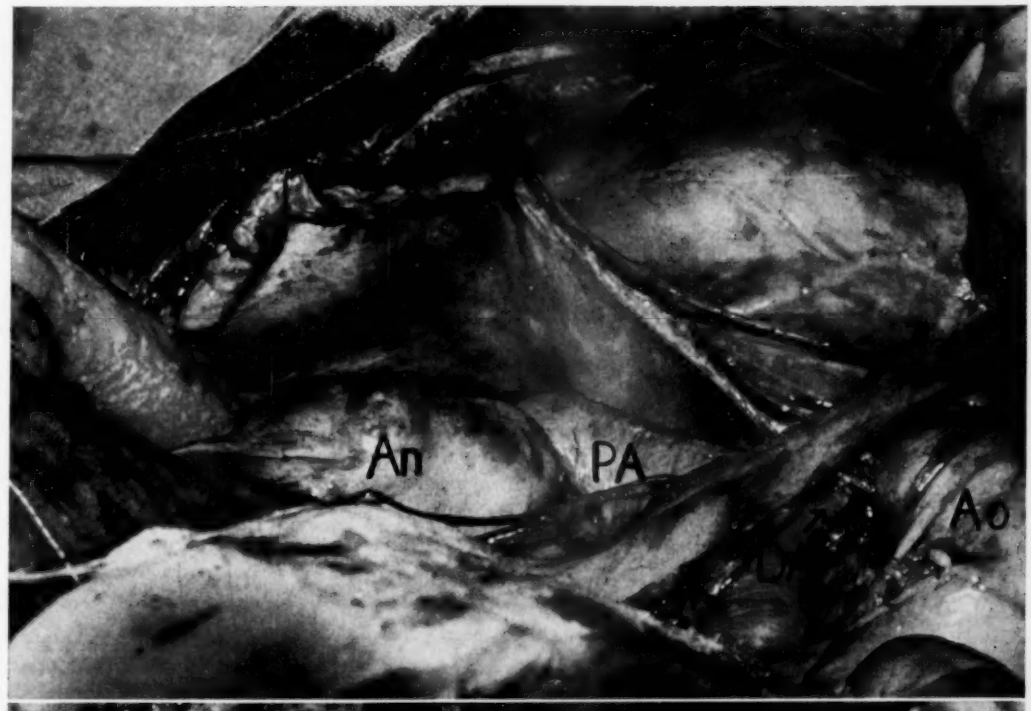


Fig. 2.—Diagram of the heart of our patient. An aneurysmal vessel from the left coronary artery enters the right ventricle. The anomaly was complicated by patency of the ductus arteriosus.

Operation.—Operation was performed on Nov. 25, 1954. A patent ductus was found, but it was unusually long and inserted more centrally on the aorta than usual, 2 cm. from the recurrent nerve. A bulge on the heart was seen through the pericardium. After the pericardium had been opened, the prominence was seen to be due to the presence of an aneurysm of the branch of the left coronary artery, beginning just to the left of the pulmonary artery and descending on the anterior aspect of the right ventricle just to the right of the interventricular septum (Fig. 2). There were a thrill, tension, and pulsation of the aneurysm, stopping immediately on compression just posteriorly and to the left of the origin of the pulmonary artery, while the aneurysm was further dilated by compressing its inferior entrance into the right ventricle (Fig. 3). The patent ductus was closed, and the afferent arterial branch to the aneurysm was dissected free and clamped while the myocardium and the ECG were observed continuously for 10 minutes. The cardiac activity and the ECG remained unchanged, and nothing abnormal could be noticed on the surface of the heart. The afferent artery was then closed by double ligation. Finally, obliteration of

Fig. 3.



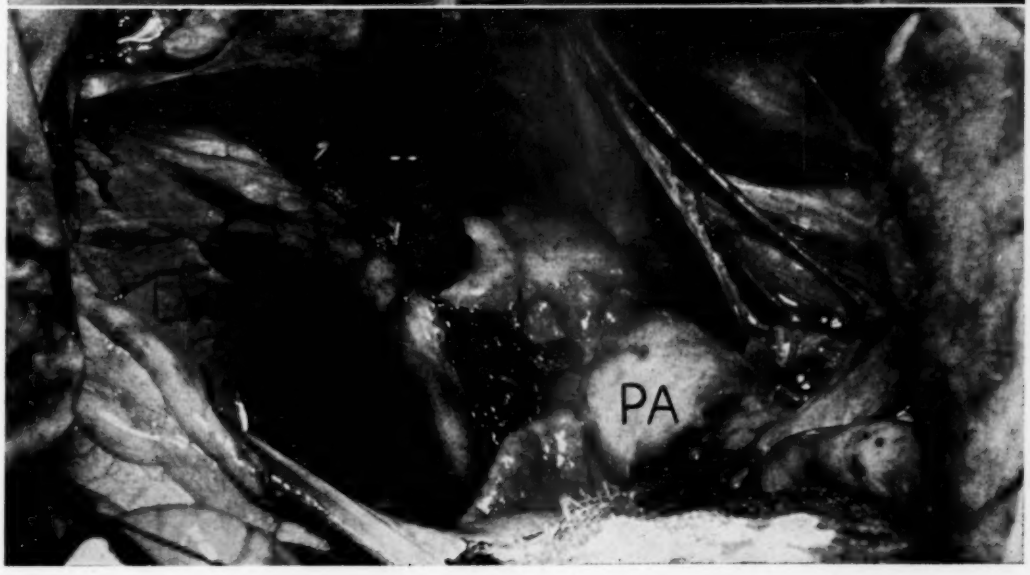


Fig. 4.

Fig. 3.—The operative field after ligation of the ductus arteriosus. It is seen how the aneurysmal vessel from the left coronary artery is dilated by compression at the site of its entrance into the right ventricle. *An* = Aneurysm. *PA* = Pulmonary artery. *Ao* = Aorta. *Pe* = Pericardium. *DA* = Ligated ductus arteriosus.

Fig. 4.—The patient was treated with ligation of the abnormal vessel from the left coronary artery at its entrance into the dilated length and undersewing of the aneurysm. *PA* = Pulmonary artery. *LV* = Left ventricle.

the inferior part of the aneurysm at the entrance into the right ventricle was attempted by means of three heavy silk sutures around the dilated vessel tied over a cushion of gelatin sponge. In this manner, the aneurysm was obliterated without thrill or pulsation (Fig. 4).

Postoperative Course.—Postoperatively, the patient's course was uneventful. During the first few days after the operation a pericardial friction rub was heard; the T waves became negative, starting in Leads I and V_{1-3} and progressing to inverted or diphasic waves in Leads I, II, and V_{1-6} (Fig. 1). These phenomena all could be ascribed to pericardial changes. Q waves did not occur. Because of the possibility of a small infarction in the anterior wall, the patient was confined to bed for 4 to 5 weeks. He was allowed up on December 29, and discharged on Dec. 31, 1954, being well.

The patient was readmitted to hospital for control catheterization 3½ months after the operation. During the first days at home the mother had observed some shortness of breath on exertion, but this had disappeared, and the patient could now follow his playmates in all pursuits, e.g., in skating. His general appearance was unchanged. His height was 135 cm.; weight was 28.2 kilograms. Clinical heart examination did not reveal any abnormalities; no murmurs were present. At heart catheterization, the blood samples did not suggest any shunts, the pressures and the cardiac output were found to be normal (Table III). The ECG had returned to normal, except for isoelectricity of the T waves in Lead I (which preoperatively were less than 0.1 mv.). Roentgen examination showed complete disappearance of the left atrial enlargement. Otherwise the findings were normal and unchanged as compared with those at the preoperative examination.

TABLE III. RESULTS OF HEART CATHETERIZATION

	BEFORE OPERATION		AFTER OPERATION	
	PRESSURE (MM. Hg)	OXYGEN SATURATION (PER CENT)	OXYGEN SATURATION (PER CENT)	PRESSURE (MM. Hg)
Pulmonary artery	23/10	85, 86, 87, 89, 88, 89, 88	71, 73, 72	26/9
Right ventricle	32/5	82, 86, 82, 81	73, 73, 74	28/4
Right atrium	6/3	81, 77	76, 73, 71	5/1
Inferior vena cava		88, 77	76, 73, 71	
Superior vena cava		75, 77	72, 73	
Femoral artery		99	95	
Oxygen uptake	166 c.c./min.		148 c.c./min.	
Peripheral blood flow	$\frac{166}{16.9 - 13.3} = 4.6$ L.		$\frac{148}{16.8 - 13.1} = 4.0$ L.	
Total pulmonary blood flow	$\frac{166}{16.9 - 14.9} = 8.3$ L.			
Arteriovenous shunt	3.7 L.			
Arteriovenous shunt to right ventricle	1.6 L.			

DISCUSSION

A preoperative diagnosis of congenital arteriovenous coronary aneurysm will rarely be possible. Ordinary roentgen examination is noncontributory, since

the very slight prominence caused by a coronary aneurysm or the calcifications of the aneurysm which have occasionally been observed[19] will scarcely be interpreted as an aneurysm, even if this possibility is borne in mind in the examination of all patients suspected of a patent ductus arteriosus. The electrocardiographic findings are normal in most cases, and the presence of ECG abnormalities is usually evidence of complicating affections.

However, a certain interest attaches to the presence of murmurs, since it appears that nearly all patients with a sizable shunt, in addition to a systolic murmur, reveal a diastolic murmur, the localization of which corresponds fairly well to that of the arteriovenous communication.[2,14] This was very distinct in our case, in which the murmur over the patent ductus arteriosus could be clearly distinguished from the pronounced, diastolic, harsher murmur over the aneurysm. In one case[16] the examiners found the murmur slightly above the shunt. Another case[11] is of interest because the diastolic murmur did not occur until the arteriovenous shunt had formed or, at least, became of functional importance; the localization of the murmur corresponded to that of the shunt. If the localization of the murmur is identical with that of patent ductus arteriosus, it will never give rise to suspicion of an aneurysm. If the diastolic murmur occurs at an unusual site, heart catheterization should be performed. The absence of shunts does not rule out the possibility of an aneurysm, since the lesion may be either a purely extracardial arteriovenous aneurysm or an aneurysm in the form of a persistent intratrabecular sinusoid without communications to the ventricles.[9] Heart catheterization will also reveal normal findings in the presence of an arterio-arterial shunt or a small shunt. (In one case[18] the murmur was of the same character as that in patent ductus arteriosus.) Even cases with a shunt to the right ventricle will scarcely arouse suspicion, and may be diagnosed as an interventricular septal defect or patent ductus arteriosus with pulmonary incompetence. If suspicion is aroused by a murmur, thoracic aortography[20] or selective angiocardiography with injection of contrast medium into the pulmonary artery may secure the diagnosis. However, the most common procedure will be thoracotomy, either because of an erroneous diagnosis or for exploratory purposes.

The present review of the literature does not give any definite information as to the prognosis of arteriovenous coronary aneurysms. Of the 9 deaths which occurred, 4 were due to extracardial diseases and 2 to cardiac failure, presumably caused by arteriosclerotic or hypertensive cardiac disease and advanced age. Two deaths were referable to cardiac anomalies, but only 1 to the arteriovenous aneurysm, which was complicated by bacterial endocarditis. The last case[11] suggests that bacterial endocarditis constitutes the principal hazard. As already mentioned, rupture into the pericardium has not been reported. If we consider all known cases of congenital aneurysms, the number is so large that we are justified in saying that the risk of rupture is very slight. On the other hand, rupture into the ventricles has been reported.[11,13]

Thus, as the prognosis is relatively favorable, it is scarcely indicated to subject these patients to operation if the anomaly can be safely diagnosed preoperatively. However, since the anomaly is usually accidentally disclosed at thoracotomy, it seems to be reasonable to employ surgical treatment if the arterio-

venous fistula can be exposed and ligated without too much difficulty and without any risk of interrupting the normal coronary circulation. On the other hand, surgical treatment is not indicated in the presence of simple aneurysms on the surface of the heart or in its intramural structures.

Finally, it is worthy of note that the mother of our patient had a violent attack of German measles during the early months of pregnancy. This disease in the mother was undoubtedly the cause of the arrested fetal development of the boy, who had both cataract and patent ductus arteriosus, which are the most frequent anomalies following German measles during pregnancy.[21,22] This also suggests that arteriovenous aneurysms are anomalies due to arrest of the normal obliteration of the intratrabecular sinusoids of the fetus.

SUMMARY

Fourteen cases of congenital arteriovenous coronary aneurysms collected from the literature are reviewed. One of these originates from our own hospital and is reported in detail. The patient was an 11-year-old boy who suffered also from patent ductus arteriosus and ocular anomalies presumably referable to an attack of German measles in the mother during pregnancy. The supposed pathogenesis of arteriovenous coronary aneurysm is considered, and the indications for surgical treatment are discussed.

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The Use of Digoxin in Infants and Children

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INTRODUCTION

Since the introduction of digoxin in a dilute solution for oral use,† administration of accurate, small doses to infants and children has been possible. However, reported pediatric experience with the drug is limited.[1,2] The following observations were made during the treatment of 86 children with digoxin at the Sharon Cardiovascular Unit and on the general medical wards of the Children's Medical Center, Boston. We are reporting the results of therapy, the toxicity encountered, and the dosages which proved effective.

PHARMACOLOGY

Digoxin, a derivative of digitalis lanata, is a purified glycoside which may be administered by the oral or parenteral route. The degree of absorption from the gastrointestinal tract has been studied by comparing the intravenous and oral dosage needed to produce the same effect.[3,4] Using this method, Wayne[3] and Gold[4] estimate that the intravenous dose is approximately two thirds of the oral one. The onset of action of the drug is moderately rapid, with a maximal effect within 6 to 8 hours after oral administration and within 2 hours after intravenous injection.[4] Recently, a new parenteral preparation has become available. This is a solution of digoxin in 40 per cent propylene glycol and 10 per cent ethyl alcohol.‡ It can be used without dilution and given intravenously or intramuscularly without local tissue damage.[5] Gold has shown that peak action of this new preparation occurs 2 hours after intravenous, and 8 hours after intramuscular administration. The fairly rapid rate of elimination of digoxin is one of its principal advantages, for if toxicity occurs, it is not as long

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†Lanoxin Elixir Pediatric, (Burroughs Wellcome).

‡Lanoxin Injection (Burroughs Wellcome).

lasting as with digitoxin or digitalis leaf. Investigators have reported toxicity as fleeting as a few hours and no longer than 24 to 48 hours.[6,7] An appraisal of the rate of dissipation of the drug was made by Batterman and DeGraff,[8] who found that 3 days after discontinuing digoxin, 87 per cent of the initial dose was gone. Slight depression in cardiac rate, however, has been reported as long as 7 days after a single digitalizing dose.[4]

CLINICAL MATERIAL AND METHODS

Eighty-six children suffering from congestive failure or an arrhythmia were treated with digoxin. Three of the patients were digitalized a second time after the drug had been discontinued, and this resulted in a total of 89 courses of digitalization. The group included 48 males and 38 females, ranging in age from newborn to 15 years. The ages of the children and the etiological classification of heart disease are seen in Fig. 1.

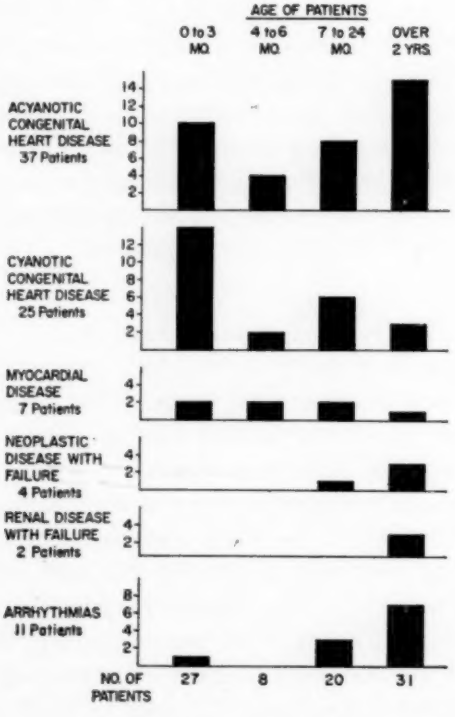

Fig. 1.—Etiological classification of 86 patients with respect to the nature of the cardiac disorder and age

Among the patients with congestive failure, congenital heart disease was the most common form of cardiac abnormality; the acyanotic variety was found more frequently than the cyanotic type. The variety of lesions is shown in Tables I and II. Myocardial disease with failure was diagnosed in 7 children. Three of these were proved to have endocardial fibroelastosis, while 4 were classified as "primary myocardial disease."[9] Congestive failure was also observed in 4 children who had neoplastic disease with involvement of the pleura or pericardium, and profound anemia, as well as in 2 patients with protracted renal disease, hypertension and severe anemia.

Arrhythmias occurred in 11 other children. Six had paroxysmal atrial tachycardia, 3 had atrial flutter with varying atrioventricular block, and 2 had long-standing atrial tachycardia. The latter 2 patients had congestive failure as well.

Indications for Therapy.—The indications for treatment with digoxin were congestive failure alone in 75 children, an arrhythmia alone in 9, and an arrhythmia with failure in 2 patients.

Methods.—Oral digoxin was administered as a pleasant tasting, lime-flavored solution containing 0.05 mg. of digoxin per cubic centimeter.* The diluent consisted principally of 11.5 per cent of alcohol in distilled water. To facilitate administration and to avoid error in dosage, a dropper containing up to 1 c.c., and calibrated in 0.2 c.c., was used. (These droppers are supplied commercially with each 2-ounce bottle of digoxin.) A small number of critically ill infants who were unable to suck or who vomited received the drug intramuscularly or intravenously.

Diuretics were not given during the period of digitalization, and low-sodium diets were not used. Oxygen was administered whenever necessary.

The oral digitalizing dose of digoxin was calculated on the basis of 0.03 ± 0.01 mg. per pound of body weight and was generally administered in one of two similar ways: either (1) 0.01 mg. of digoxin per pound at 6- to 8-hour intervals until an adequate clinical response was obtained or digitalis toxicity was noted, or (2) 0.02 mg. of digoxin per pound and then 0.01 mg. per pound at 6- or 8-hour intervals until therapeutic effects or toxicity appeared. Parenteral dosage was calculated at two thirds of the oral dose.[3,4]

Name_____ Age_____ Height_____ Weight_____

Date	Weight	Heart Rate	Respiratory Rate	Blood Pressure	Liver	Neck Veins	Edema	Râles	Cyanosis	Vomiting		ECG	X-Ray	Digoxin Dose	Times Given	Other Therapy	Remarks

Fig. 2.—Chart used for following patients on digoxin.

Daily maintenance dosage was estimated to be one quarter to one third of the initial digitalizing dose and was given in two equally divided doses at 12-hour intervals. If clinical improvement did not persist, the daily dose was increased until the patient's status was satisfactory or until clinical or electrocardiographic signs of toxicity appeared.

Throughout the period of digoxin administration electrocardiograms were taken frequently and were analyzed for rate, rhythm, P-R and Q-T intervals, and S-T segment and T-wave changes. Daily notes were made of the patient's weight, cardiac and respiratory rates, and liver size. The presence of neck vein distention, cyanosis, and vomiting was also noted. Because the chart

*Lanoxin Elixir Pediatric (Burroughs Wellcome).

used for recording these findings proved to be useful in following the patient's course, it is reproduced in Fig. 2. The response to the drug was based on the above observations and was considered to be either good, fair, or poor. If all signs of congestive failure disappeared, the result was classified as good. If evidence of congestive failure lessened but did not disappear, the response was called fair. If no improvement occurred or if the patient deteriorated, the result was classified as poor. In the cases of arrhythmia we considered the result good if the sinus pacemaker was reinstituted or, at least, the ventricular rate was reduced to a normal level.

TABLE I. INCIDENCE OF ACYANOTIC CONGENITAL HEART DISEASE

Ventricular septal defect	10
Patent ductus arteriosus	4
Atrioventricularis communis	4
Tetralogy of Fallot with failure post-Potts procedure*	4
Ostium primum defect	3
Congenital mitral stenosis	2
Cor triatriatum	2
Congenital aortic stenosis and insufficiency	1
Atrial septal defect and partial anomalous pulmonary venous drainage	1
Atrial septal defect with failure following closure of the defect	1
Coarctation of the aorta	1
Coarctation of the aorta and aortic stenosis	1
Mitral valve and left ventricle hypoplasia and coarctation of the aorta	1
Tetralogy of Fallot with failure post-Blalock procedure*	1
Tetralogy of Fallot with failure post-Brock procedure*	1
Total	37

*These patients were acyanotic at the onset of failure which was caused by an excessively large left-to-right shunt.

TABLE II. INCIDENCE OF CYANOTIC CONGENITAL HEART DISEASE

Truncus arteriosus	4
Total anomalous pulmonary venous drainage	4
Tricuspid atresia	3
Ventricular septal defect with bidirectional shunt	3
Transposition of the great vessels	2
Pulmonary atresia	1
Ventricular septal defect with coarctation of the aorta and distal patent ductus arteriosus	1
Coarctation of the aorta and distal patent ductus arteriosus and mitral stenosis	1
Ebstein's anomaly of the tricuspid valve with coarctation of the aorta and distal patent ductus arteriosus	1
Aortopulmonary fenestration with bidirectional shunt	1
Inferior vena caval drainage into the left atrium	1
Undiagnosed cyanotic congenital heart disease	1
Total	23

OBSERVATIONS

A. *Results of Therapy.—*

1. *Clinical response:* The clinical response to digoxin is shown in Fig. 3. Of the 37 patients with acyanotic congenital heart disease, the response was almost evenly divided among good, fair, and poor. The response of the cyanotic group showed a smaller proportion of good results. The children with myocardial disease had a variable response. Two of the 7 patients could not be given average doses of digoxin because of unusual sensitivity to the drug. As might be expected, therapy was not very beneficial for the terminal failure of those with neoplastic disease and anemia. The 2 children with hypertension and anemia secondary to long-standing renal disease were treated for acute congestive failure with pulmonary edema, and in both a dramatic improvement occurred within a few hours after institution of therapy.

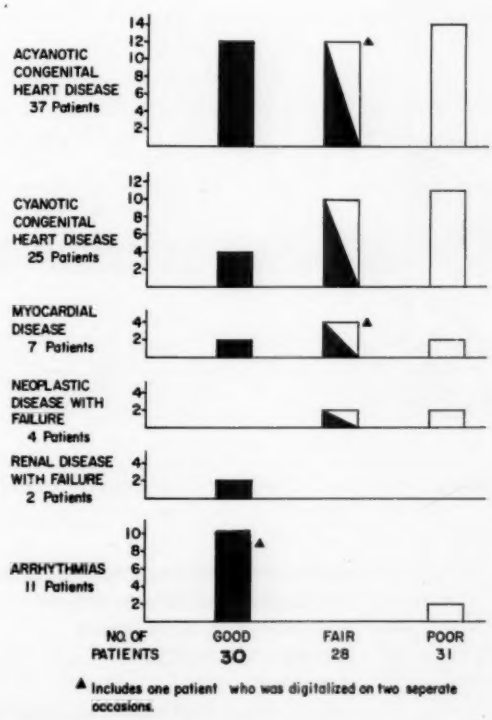

Fig. 3.—The clinical response to 89 courses of digoxin in 86 patients.

The response of the 6 children with paroxysmal atrial tachycardia was uniformly good. Four of the patients reverted to normal sinus rhythm within the first 24 hours of digoxin administration, one on the third day of treatment, and the sixth patient reverted to sinus rhythm on vagal stimulation after digitalization was complete. Of the 3 patients with atrial flutter 1, aged 4 days, reverted to sinus rhythm after 2 days of digoxin therapy[10] (Fig. 4). The other 2 did not respond to digoxin alone, but when quinidine was added, the arrhythmia disappeared in both. In the 2 children with chronic atrial tachycardia and

marked congestive failure, the signs of failure disappeared after 36 hours in one and 72 hours in the other. Their further hospital courses are discussed in the section on toxicity.

2. *Electrocardiographic changes:* A survey of the electrocardiographic changes is presented in Fig. 5. A drop in rate of 30 or more per minute was considered to be a significant change. If the Q-T interval was of normal duration at the start of therapy and became at least 0.03 second shorter than the average value for the cardiac rate during treatment, it was arbitrarily considered to have shortened.

The drop in rate was the most reliable electrocardiographic indication of effective digitalization. Most of the patients with good clinical response showed a significant slowing of the heart rate.

B. *Toxicity.*—

1. *Clinical evidence:* As stated earlier, digoxin was used in increasing doses until a good clinical response occurred or until evidence of toxicity appeared

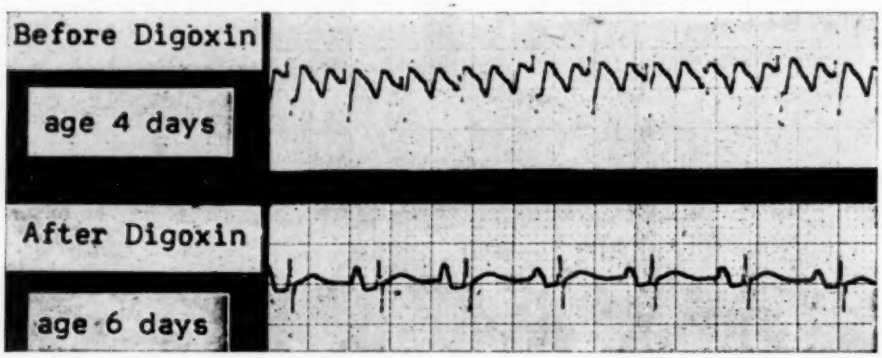

Fig. 4.—Atrial flutter with a changing 2:1 and 3:1 atrioventricular block in a 4-day-old baby, with reversion to normal sinus rhythm 2 days after the commencement of digoxin therapy.

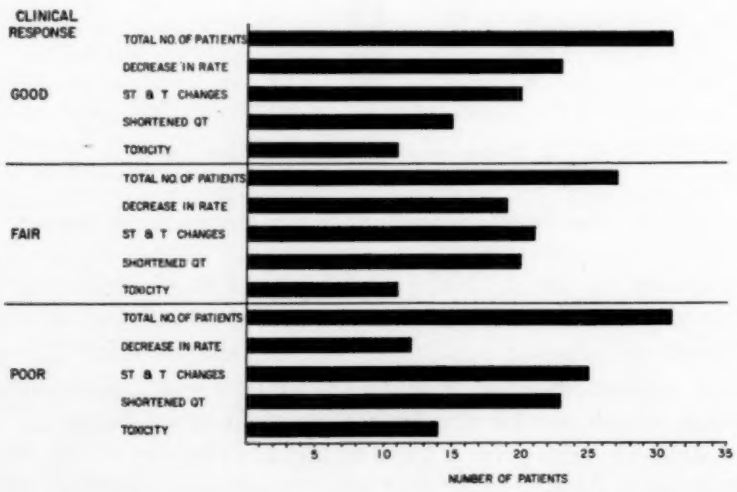

Fig. 5.—The electrocardiographic changes seen during the treatment of 86 children with digoxin.

either clinically or on the electrocardiogram. The symptoms and signs of toxicity proved to be of particular interest, since the classic picture of digitalis intoxication as seen in the adult was not often found. Anorexia proved difficult to judge accurately in a group of sick, hospitalized children. However, it was the general impression that it did not appear more frequently in this group of patients than in others who were not on digoxin. A few of the older children complained of nausea. Vomiting occurred in 45 patients. It was most marked in 13 children who also had electrocardiographic signs of toxicity. In another 25, vomiting was mild and unaccompanied by any other evidence of intoxication. In the remaining 7 children, vomiting could be attributed to causes other than administration of the glycoside. In no case could death be ascribed to digitalis intoxication.

2. *Electrocardiographic evidence:* The electrocardiogram proved to be the most valuable and often the only guide for the detection of toxicity in this age group. Thirty-six patients had electrocardiographic abnormalities indicative of digitalis intoxication. These abnormalities are listed in Table III. It may be seen that disturbances in atrioventricular conduction and sinoatrial node depression were common. Twenty-eight children had first degree heart block; in 12 of

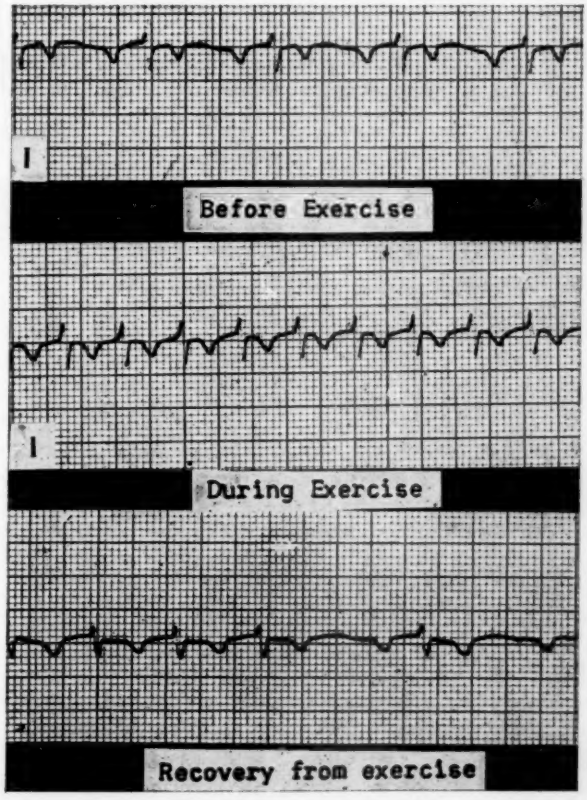

Fig. 6.—Lead I. The effect of exercise in a patient with atrial tachycardia and 2:1 atrioventricular block induced by digoxin. During exercise the 2:1 block disappears and there is a 1:1 atrioventricular response.

these there was other evidence of digitalis intoxication, but in 16 no other signs of toxicity were present and the P-R interval was under 0.20 second. While the patients in this latter group have been classified as having toxicity, they might perhaps be regarded with equal justification as showing only good digitalis effect. Ectopic beats were found in 10 patients. Nodal rhythm occurred in 3 patients, interference dissociation in 2, and atrial fibrillation in 1. The frequency with which toxicity appeared in the groups having different clinical responses is shown in Fig. 5, while Table IV relates toxicity to the underlying heart disease of the patients.

The duration of toxic manifestations is noteworthy because in all cases the abnormality disappeared within 6 to 48 hours after cessation of digoxin.

3. *Special circumstances under which toxicity appeared:* Of 7 children with myocardial disease, 2 showed an unusual sensitivity to digoxin.

D.M., an 8-year-old boy, was in mild congestive failure on admission to Children's Medical Center. Electrocardiograms prior to digitalization showed extremely low voltage with S-T and T-wave changes as well as occasional ventricular ectopic beats. Digoxin, 0.02 mg. per pound, was used for digitalization and was well tolerated until the last of four divided doses was given. Following the final dose, he vomited and had frequent ventricular ectopic beats. Maintenance was attempted with extremely small doses of digoxin, but bigeminy or frequent ventricular ectopic beats persistently appeared. No other digitalis preparations were tried.

TABLE III. ELECTROCARDIOGRAPHIC ABNORMALITIES OBSERVED IN 36 PATIENTS

ABNORMALITY	NUMBER OF TIMES OBSERVED
First degree atrioventricular block	28
(P-R less than 0.20 second 16)	
(P-R greater than 0.20 second 12)	
Second degree atrioventricular block (Wenckebach phenomenon 5)	11
Sinus pause and nodal escape	5
Ectopic beats	
Atrial	3
Nodal	3
Supraventricular (could not be further characterized)	1
Ventricular	3
Nodal rhythm	3
Interference dissociation	2
Atrial fibrillation	1

TABLE IV. UNDERLYING HEART DISEASE IN 36 PATIENTS WHO DEVELOPED DIGITALIS TOXICITY

UNDERLYING HEART DISEASE	NUMBER OF PATIENTS WITH TOXICITY	TOTAL NUMBER OF PATIENTS
Acyanotic congenital heart disease	14	37
Cyanotic congenital heart disease	10	23
Myocardial disease	5	7
Neoplastic disease with failure	2	4
Renal disease with failure	1	2
Arrhythmia	4	11

O.G., a 20-month-old boy who later proved to have endocardial fibroelastosis, mitral stenosis, and coarctation of the aorta, was started on digitoxin at 8 months of age and showed no sign of toxicity. At the age of 19 months the drug was discontinued and failure reappeared. Approximately half of the usual digitalizing dose of digitoxin was given but was not continued because of bradycardia. Ten days later he entered the Children's Medical Center in severe congestive failure. A small initial dose of digoxin, 0.03 mg. (i.e., 0.0015 mg. per pound), was given. Within 4 hours the cardiac rate, which had been 116 per minute while he was sleeping, dropped to 76 per minute. After 24 hours tachypnea disappeared and the liver decreased in size. Over the next 6 days he was maintained on an average dose of 0.04 mg. of digoxin and remained out of failure. However, on the seventh day his pulse was slow and irregular. The electrocardiogram revealed a cardiac rate of 50 per minute with sinus arrhythmia and frequent sinus pause, nodal escape, and wandering atrial pacemaker, as well as rare ventricular premature beats. Digoxin was discontinued temporarily, and after 24 hours normal sinus rhythm reappeared. The child died 1 week later in congestive failure which was unresponsive to therapy.

A second aspect of toxicity concerned the management of 2 children in whom an arrhythmia could be controlled only on digoxin doses which produced electrocardiographic evidence of toxicity. In one child this electrocardiographic abnormality was mild, while in the other it probably represented a more advanced form of intoxication. Extremely close observation and manipulation of dosage prevented any more serious consequences.

In the case of S.L.T., a 20-month-old girl with an atrial tachycardia of at least 1 month's duration and marked congestive failure, digoxin therapy resulted in complete clearing of failure within 36 hours. At that time the electrocardiogram revealed sinus rhythm alternating with runs of ectopic atrial beats, which were more frequent when the patient became excited. Maintenance doses were increased until the ninth hospital day, when the patient received 0.08 mg. digoxin every 6 hours, i.e., a total daily dose of 0.32 mg. for a child of 21 pounds. This dosage was continued, and the electrocardiogram revealed a few ectopic atrial beats, very slightly prolonged P-R interval, sinus rhythm, and nodal beats. After 11 days on 0.32 mg. of digoxin daily, ectopic atrial beats were seen only when the child was extremely agitated. Frequent sinus pauses, considered to be a mild form of toxicity, persisted. Dosage was then reduced to 0.10 mg. every 8 hours. She was discharged on this dose and remained symptom free. Three months later the electrocardiogram continued to show a slightly prolonged P-R interval and occasional sinus pauses.

The second child, D.W., a 7-year-old boy who weighed 44 pounds, re-entered the hospital with congestive failure of 1 week's duration. He was known to have an atrial tachycardia which had been resistant to therapy for at least 17 months. On entry he received 0.04 mg. of digoxin per pound for a digitalizing dose and vomited once during this period. At the end of 36 hours signs of congestive failure had decreased and the electrocardiogram revealed a variable atrioventricular block (predominantly 2:1) with a ventricular rate of 80 per minute, but rising at times to 160 to 180 per minute with disappearance of block. The 1:1 atrioventricular response appeared when the patient exercised or became excited, so that during much of the day his pulse was excessively rapid (Fig. 6). Since atrioventricular block, a form of digitalis toxicity, was needed for any measure of control of the tachycardia, digoxin was stopped and quinidine begun. However, this broadened the QRS considerably and, so, was discontinued. Because digoxin had been found to slow the heart rate, although at the same time to produce toxicity, it was restarted in a dose of 0.5 mg. daily in four divided doses. Block again appeared intermittently. Because of reversion to a 1:1 atrioventricular response with excitement or activity, a tranquilizer (Serpasil*) was given. This resulted in persistence of the 2:1 block during most of the day and a relatively normal ventricular rate. Sixteen months after his hospitalization normal sinus rhythm appeared.

*Proprietary preparation of reserpine (Ciba).

Medication was then discontinued and he remained well for 1 year. At the end of that time the atrial tachycardia recurred. It should be mentioned that during the first period of digoxin administration the patient developed a left-sided hemiplegia. Fig. 7 shows the electrocardiograms before, during, and after combined therapy with digoxin and Serpasil.

Lowered body stores of potassium may have played a role in the development of toxicity in 2 patients.

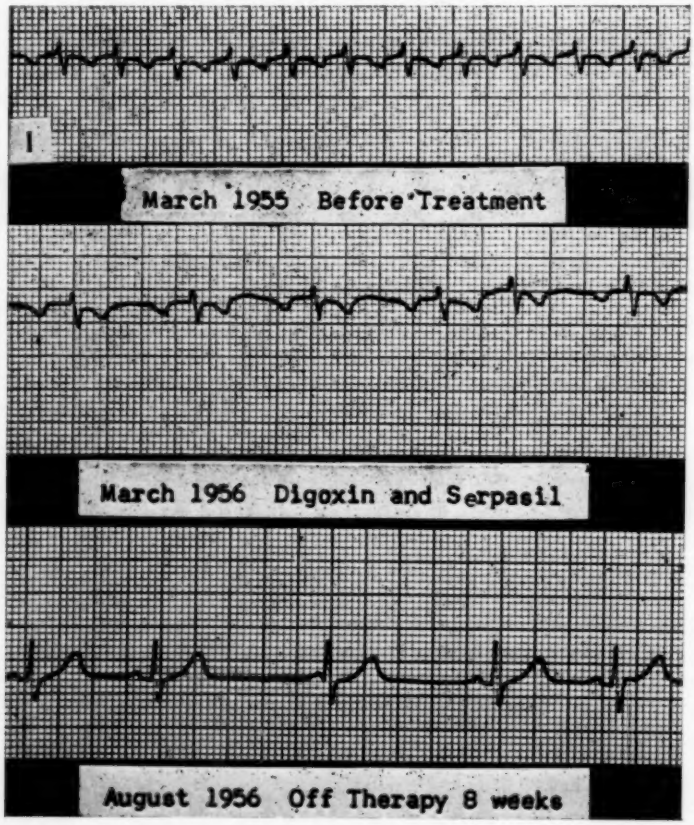

Fig. 7.—Lead I. The electrocardiograms in a patient with a history of tachycardia of 17 months' duration. Note the rapid rate and inverted P before treatment. After digoxin and Serpasil were given there is persistence of the atrial pacemaker, but 2:1 atrioventricular block results in a slower ventricular rate. Tracing in August, 1956, reveals normal sinus rhythm with occasional sinus pause and nodal escape.

One patient, D. C., a 21-day-old boy with coarctation of the aorta and a distal patent ductus arteriosus, developed congestive failure and was treated with digoxin but experienced only partial relief in failure. Mercuhydrin*, 0.1 c.c., was then given intramuscularly but no change ensued. The serum chloride level was found to be 81 mEq. per liter, and he was started on ammonium chloride. Two days later a second injection of Mercuhydrin was given, with diuresis of approximately 6 per cent of his body weight. The congestive failure improved, but an electrocardiogram revealed frequent sinus pauses with nodal escape and wandering atrial pacemaker. Oral potassium was begun and within 24 hours the cardiac rhythm returned to normal.

*Proprietary preparation of meralluride (Lakeside).

A second child, P.M., a 9-year-old girl with tetralogy of Fallot, and weighing 40 pounds, developed severe congestive failure 6 months after Potts' procedure. She received very little help from digoxin, which was increased until there was slight prolongation of the P-R interval. Improvement occurred only with the additional, daily administration of ammonium chloride and potassium chloride, and Mercuhydrin twice weekly. She did moderately well for the next 8 months on this program, although eating very little. Because of her general improvement all

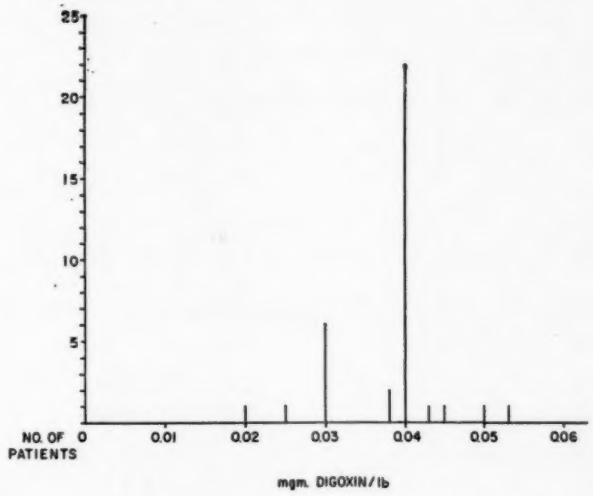

Fig. 8.—Digitalizing doses of digoxin in children up to 2 years of age. Toxic doses are not included.

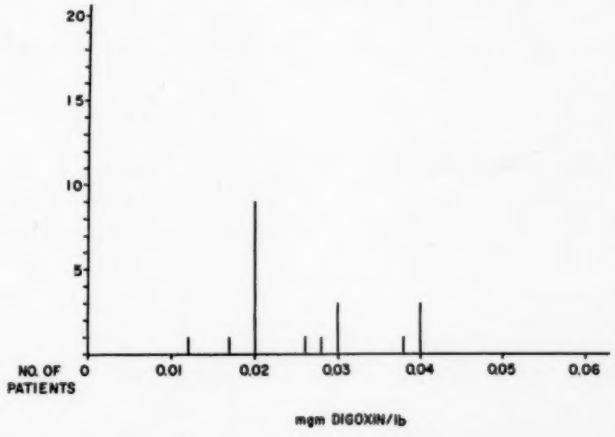

Fig. 9.—Digitalizing doses of digoxin in children 2 to 15 years of age. Toxic doses are not included.

drugs but digoxin were discontinued and Diamox* was added. Her appetite continued to be poor, and severe failure reappeared in 2½ weeks. An electrocardiogram at that time revealed atrial fibrillation with frequent premature ventricular beats. Serum potassium was 4.5 mEq. per liter. Digoxin and Diamox were stopped. Within 2 days normal sinus rhythm returned.

It would seem likely that the patient developed digitalis toxicity on a high dose of digoxin, which she could tolerate only while receiving potassium chloride.

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*Proprietary preparation of acetazoleamide (Lederle).

TABLE V

AGE	DIGITALIZING DOSE		MAINTENANCE DOSE (AS A PROPORTION OF THE DIGITALIZING DOSE)	
	AVERAGE	RANGE	AVERAGE	APPROXIMATE RANGE
0 to 2 yr.	0.04 mg./lb.	0.02 to 0.05 mg./lb.	1/3	¼–½
2 to 15 yr.	0.02 mg./lb.	0.12 to 0.04 mg./lb.	1/3	¼–½

TABLE VI.

Digitalizing Doses Producing Toxicity (Excluding Doses Which Produced P-R Prolongation under 0.20 second)

	Number of patients	*Mg. of digoxin/lb. of body weight*
Children 0 to 2 years of age	1	0.034
	1	0.040
	1	0.043
	1	0.053
Children 2 to 15 years of age	1	0.020 (D.M.)
	1	0.035
	1	0.040
	1	0.041
	1	0.083
Maintenance Doses Producing Toxicity		
Children 0 to 2 years of age	1	0.0014 (O.G.)
	1	0.009
	3	0.010
	1	0.012
	2	0.015
	1	0.016
	1	0.040
Children 2 to 15 years of age	1	0.001
	1	0.002
	3	0.003
	1	0.005
	1	0.006
	1	0.007
	1	0.008
	2	0.009
	1	0.011
	1	0.012

DOSAGE

Figs. 8 and 9 illustrate the dosage of oral digoxin which was used during the first 24 hours of administration of the drug, with the exclusion of all patients who showed any evidence of toxicity. The oral maintenance doses which were used are shown in Figs. 10 and 11. A summary of these findings is given in Table V.

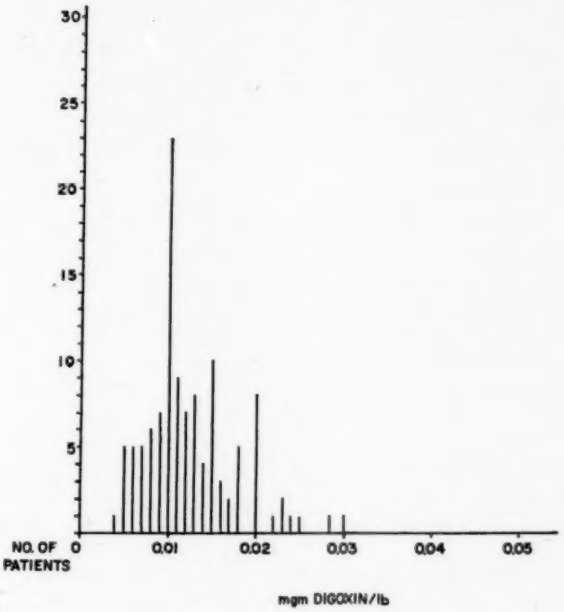

Fig. 10.—Maintenance doses of digoxin in children up to 2 years of age. Toxic doses are not included.

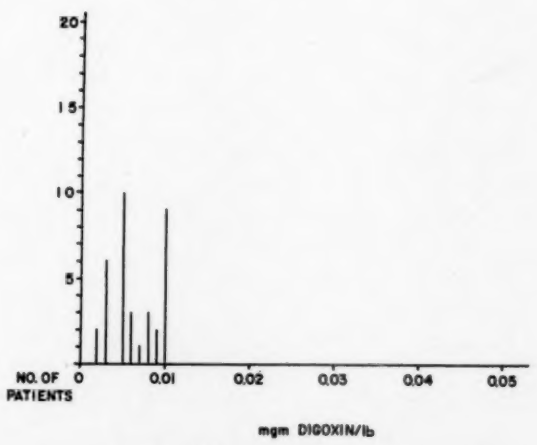

Fig. 11.—Maintenance doses of digoxin in children 2 to 15 years of age. Toxic doses are not included.

Dosage on which digitalis toxicity appeared electrocardiographically are shown in Table VI. Patients with slight prolongation of the P-R interval (i.e., P-R was under 0.20 second) are not included, however. Unusual sensitivity to digoxin was found in Patients D.M. and O.G., as mentioned previously.

DISCUSSION

In this series children with congestive failure and arrhythmias responded variably to the administration of digoxin. On the whole, the cyanotic group responded least well and the patients with paroxysmal atrial tachycardia best. Although congestive failure was often marked and the underlying heart disease severe, especially in the cyanotic infant group, the judicious use of digoxin in increasing amounts produced considerable amelioration of symptoms in many. In some cases, particularly in the unusual arrhythmias, no adequate therapeutic effect could be achieved without producing toxicity.

The most helpful index of digitalis toxicity was the electrocardiogram. Among the electrocardiographic signs of toxicity, atrioventricular conduction disturbances, sinoatrial node depression, and supraventricular arrhythmias were common, in contrast to the ventricular ectopic beats which are found more frequently in adults. In light of our experience and that of others,[11] it seems wise to recommend that signs of digitalis toxicity be particularly sought in patients in whom body potassium may be changing.

We cannot emphasize enough our belief that although most children may be digitalized and maintained on a relatively set schedule, depending on age and weight, the great variation in response requires individualization of dosage, and that digoxin should be administered until therapeutic effects are achieved or toxicity appears.

The results we obtained with oral digoxin are generally comparable to those observed in a previous study with digitoxin.[12] However, we felt that the fairly rapid elimination of digoxin and the consequent short duration of toxicity permitted us to use it more liberally. In some cases, cautious yet rapidly progressive increases in digoxin produced prompt improvement in the patients. With a longer-acting preparation such a procedure would have been slower and might have been more dangerous. We found that vomiting was more prevalent in the children on digoxin, but this was not a major factor in management and, therefore, we consider it only a slight disadvantage as compared to those of digitoxin. The second disadvantage, that of losing all effect of digoxin if it is inadvertently discontinued at home, proved negligible in our study. Careful instruction of parents was fruitful in avoiding this, we feel.

SUMMARY

1. Eighty-six children with congestive failure or arrhythmias were treated with digoxin. Two separate courses of therapy were given to 3 patients.

2. Dosage for digitalization of patients up to 2 years of age was found to be approximately 0.04 mg. per pound of body weight in 24 hours. Children over 2 years of age required approximately 0.02 to 0.03 mg. per pound of body weight for digitalization. Maintenance in both groups could be achieved, generally, with the daily administration of one third of the digitalizing dose.

3. Exceptions to this schedule made it mandatory that each patient's digitalization be individualized.

4. Definite clinical or electrocardiographic evidences of toxicity were observed in 22 patients, in many of whom excessive dosage was deliberately given in an attempt to achieve therapeutic results. The toxicity was mild in most and reversible in all.

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Ouabain on the Hypothermic Dog Heart

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The increased use of hypothermia in medicine and surgery has emphasized the need for more fundamental information on the physiology and pharmacology of the hypothermic heart. Digitalis glycosides are frequently used in patients who are subsequently subjected to surgery under hypothermia, despite the limited information available on the effect of these compounds on the hypothermic myocardium.[1-3] Previous studies made in this laboratory on the cardiac electrolyte balance and sensitivity to calcium[4,5] suggested that digitalis might affect the hypothermic myocardium unfavorably regarding its susceptibility to ventricular fibrillation. In the experiments reported here, dogs were digitalized with ouabain, and various approaches were employed in an attempt to define the effect of digitalization in hypothermia.

METHODS

A total of 76 mongrel dogs of both sexes, weighing from 8 to 18 kilograms, were used. Hypothermia was induced by immersion in an iced bath. Details of the method have been described previously.[6] The heart temperature was measured thermoelectrically through an esophageal electrode. Comparative measurements in many animals showed that esophageal temperatures, near the heart level, did not differ by more than $\pm$ 0.6° C. from temperatures measured concurrently with a jugular catheter-thermoelectrode at the lumen of the right atrium. Blood pressures were measured via a mercury manometer. Electrocardiograms were recorded on a Sanborn Viso-Cardiette and continuously monitored through a DuMont oscilloscope. Ouabain powder was dissolved in saline just before use and injected or infused via the jugular vein. For the series of experiments involving hypothermic surgery, dogs were digitalized with ouabain (0.01 to 0.02 mg./Kg.) and cooled to heart temperatures of 25° $\pm$ 1° C. under continuous artificial respiration; the latter was controlled to maintain an approximately normal pH. Subsequently, the animals were subjected to thoracotomy and 15-minute venous occlusion. During this time right ventriculotomy and ventriculoraphy were performed. The surviving animals were rewarmed to heart temperatures of from 33 to 35° C., and their ability to respire spontaneously was taken as the end-point for survival. A group of nondigitalized controls were treated similarly.

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RESULTS

Spontaneous Hypothermic Fibrillation.—The incidence of spontaneous ventricular fibrillation (VF) in the control and digitalized animals cooled to terminus is shown in Table I. Digitalization was achieved with ouabain in doses of 0.01 to 0.1 mg./Kg., i.v., prior to induction of hypothermia. The larger doses were used in order to determine all possible actions, since experiments with the smaller doses did not produce any obvious effect. Even with the larger doses the incidence of VF was not altered significantly (Table I). However, the data suggest that asystole occurs at higher temperatures in digitalized animals than in similarly treated controls. To eliminate the unknown vagal effects of digitalis glycosides, a few animals were given atropine sulfate (0.1 mg./Kg.) prior to digitalization and cooling. The results (included in Table I) show that the terminal events in this latter group were similar to those in the controls.

In the absence of parasympathetic blockade a number of digitalized animals which terminated in asystole at relatively high temperatures were found to respond to periodic electrical stimuli applied directly to the ventricle (artificial electrical pacemaker). Thus, the blood pressure was restored and a few animals were cooled to very low temperatures (16 to 14°C.) despite spontaneous asystole at 22 to 18°C. Other animals, however, terminated in VF during the application of the driving stimuli. Untreated animals terminating in asystole at low temperatures did not respond to direct electrical stimuli, and, in general, electrical stimulation was not effective below 16 to 14°C. in either group.

Ouabain Toxicity.—Determinations were made of the dose of ouabain required to produce extrasystolic action and fibrillation within 1 hour after injection. In 5 normothermic controls, 0.02 mg./Kg. was followed by extrasystolic action within 15 to 30 minutes. By contrast, 10 hypothermic animals were apparently unaffected by doses as large as 0.1 mg./Kg. But with dosage in the range 0.15 to 0.25 mg./Kg., 5 hypothermic dogs responded with extrasystoles and VF. In all the hypothermic animals the ouabain was administered after temperature stabilization at 27° ± 1° C. for 1 hour.

It was of interest to note that animals which showed ventricular arrhythmias following the larger doses of ouabain, prior to hypothermia, reverted to normal rhythm on subsequent cooling when the heart temperature reached 33 to 30°C. In this connection it has been a general observation in this laboratory that spontaneous ventricular extrasystoles (seen in occasional dogs before cooling) disappear completely at heart temperatures below 35°C.

TABLE I. HYPOTHERMIC DEATHS OF DIGITALIZED ANIMALS

	CONTROLS	ATROPINE	OUABAIN	OUABAIN AND ATROPINE
Number of Animals	10	5	10	5
Fibrillating	6	3	4	3
Temp. (degrees C.)	20.7	21.2	22.0	20.2
Asystolic	4	2	6	2
Temp. (degrees C.)	16.5	17.3	19.2	16.9

Fibrillation Under Cardiac Surgery.—Cardiac surgery under hypothermia was performed, as described under *Methods*, in control and digitalized animals. All animals which succumbed during the procedure terminated in VF. There were no deaths due to congestive heart failure nor was there any evidence suggesting this condition as reported by Lombardo and associates.[3] Furthermore, ventricular fibrillation was taken as the end-point, and no attempts were made to resuscitate these animals. The incidence of VF in each group is given in Table II. An index of susceptibility to fibrillation can be obtained by classifying the animals into four groups as indicated in the legend of Table II. It is apparent that the majority of the animals fibrillated early during the course of ventriculotomy, regardless of previous treatment. Generally, mechanical stimulation (especially of the endocardium and the interventricular septum) and/or tissue injury seem to have been the main inciting causes, since the majority of the animals which fibrillated did so early rather than late in the period of inflow occlusion. Therefore, circulatory stasis and possible anoxia would appear not to be primary factors. This was also found to be the case regardless of the anesthetic used.[7]

TABLE II. RIGHT VENTRICULOTOMY IN HYPOTHERMIC* DIGITALIZED DOGS

	CONTROLS	OUABAIN
Number of Animals	10	10
Survived	4	3
Fibrillated	6	7
Group I	3	3
Group II	3	3
Group III	0	1
Group IV	0	0

*Esophageal temperature, 25° ± 1°C.
Group I: Fibrillated immediately on ventricular incision.
Group II: Fibrillated later during surgical manipulation of the heart.
Group III: Fibrillated after completion of cardiac surgery but immediately (0 to 2 min.) after release of inflow occlusion.
Group IV: Fibrillated during rewarming.

DISCUSSION

Previous studies indicated that the hypothermic myocardium may accumulate calcium,[4] and that its susceptibility to exogenous calcium is increased considerably.[5] On the basis of the hypothesis that cardiac glycosides owe at least part of their activity to an influence on the calcium balance across the myocardial cell membrane,[8] it might be anticipated that the hypothermic heart would be more sensitive to the action of ouabain. This has not been substantiated by the present experiments. Spontaneous VF did not occur with greater frequency in digitalized hearts under progressive hypothermia, and the digitalized hypothermic animals were no more susceptible to surgical manipulations of the heart than the nondigitalized controls (Table II). In fact, the susceptibility of the heart to ouabain-induced arrhythmias was decreased with hypothermia. This was true

even for doses of ouabain which were relatively large in comparison to therapeutic doses. A similar conclusion of hypothermic desensitization to digitalis was reached by Satoskar and Trivedi,[1] who infused Digilanid into cats subjected to hypothermia.

Differences in the terminal temperatures between controls and digitalized animals (due to the incidence of asystole at relatively high temperatures) can be attributed to the well-known vagal effects of digitalis compounds, since these differences are not manifested in atropinized digitalized animals (Table I). The responsiveness of the arrested heart to a ventricular electrical pacemaker lends further support to this view.[9]

Although hypothermia itself increases the suceptibility to VF, a concurrently increased susceptibility to the action of arrhythmia-inducing chemical agents does not necessarily follow. Thus, the increased susceptibility of the hypothermic heart to calcium-induced VF appears to be relatively specific for calcium. The results reported here emphasize that the relationship between the action of digitalis glycosides and calcium balance across the myocardial membrane is more complex than can be accounted for by a simple hypothesis of altered calcium balance.

It is generally accepted that digitalis glycosides induce a loss of potassium from the myocardial fiber, and that increased intracellular concentrations of potassium result in decreased digitalis toxicity.[8] If this can be applied to hypothermic hearts, the present results would suggest that the intracellular concentration of myocardial potassium is increased under hypothermia. This conclusion is not in accord with the evidence provided by direct measurements of A-V electrolyte differences.[4] It must be pointed out, however, that the latter experiments provided information on the potassium balance of the myocardium at a single temperature (26 to 24°C.) and, therefore, give little information regarding changes which may have occurred earlier in the course of hypothermia.

Regarding the electrophysiologic properties of the heart, it should be noted that digitalis has an effect opposite to that of hypothermia[11] on the ventricular refractory period.[10] The former shortens this period while the latter lengthens it. This, then, may serve as the basis of the antagonism of digitalis toxicity by cold. Nevertheless, a complete analysis of the mechanisms through which various agents affect the myocardium in relation to susceptibility to arrhythmias and fibrillation cannot be made with the presently available information. The present data are offered as a contribution to this general problem and indicate that the arrhythmia-inducing effects of hypothermia and digitalis are not additive but, rather, antagonistic; by contrast, those of hypothermia and calcium are additive and probably synergistic.[5] In this connection it is pertinent to note that Smith, Hoff and Winkler[12] have shown in normothermic dogs that the digitalized heart is no more susceptible to infused calcium than the nondigitalized organ. By contrast, Gold and Edwards[13] reported an increased toxicity of ouabain in hypercalcemic animals.

Lombardo and associates[3] reported that a large proportion of dogs undergoing right ventriculotomy under hypothermia developed signs of right ventricular failure, which were partially avoided by prior digitalization with acetyl

strophanthidin. These animals were under Pentothal anesthesia and were hyperventilated. In view of the fact that congestive failure has not been found to occur in hypothermic surgery when pentobarbital anesthesia and controlled ventilation are used,[7,14,15] it would appear that the cardiac failure observed by these authors is associated with the nature and/or amount of anesthetic used, and possibly overventilation. The degree of positive intrathoracic pressure produced by artificial respiration may also have been a factor.

SUMMARY

The effect of digitalization with ouabain on the susceptibility of the hypothermic heart to ventricular fibrillation (VF) was tested in dogs. Spontaneous VF did not occur with greater frequency in digitalized animals than in controls. Similarly, ouabain did not alter significantly the incidence of VF during experimental ventriculotomy under hypothermia.

Digitalized animals had a tendency to terminate in asystole at higher temperatures than the controls, but this difference was eliminated by pretreatment with atropine, suggesting a parasympathomimetic action of ouabain. Hearts in asystole at relatively high temperatures (22 to 18° C.) responded to electrical pacemakers. In contrast, hearts undergoing asystole at low temperatures (16 to 14° C.). were generally unresponsive to electrical stimuli.

Hypothermia protected against the arrhythmic effects of toxic doses of ouabain. The dosage which produced arrhythmias at normal body temperature was found to be only one fifth of that required in hypothermia (27° ± 1° C.).

In general, the results suggest that the arrhythmic effects of hypothermia and digitalis are not synergistic but, rather, antagonistic. Thus, digitalization per se is not a contraindication to hypothermia.

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Evaluation of Antihypertensive Effects of S.9-390 (2-(o-Chlorobenzyl) Imidazoline Hydrochloride)

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INTRODUCTION

In patients with severe hypertension the need still exists for drugs which will give satisfactory blood pressure control with less toxic effect than that experienced with currently available antihypertensive agents. The new antihypertensive agent S.9-390* has been evaluated as a part of our continued search for such effective, nontoxic, oral antihypertensive agents.

MATERIALS AND METHODS

Ten patients with severe hypertension were chosen for study. These included 9 men and 1 woman, whose ages ranged from 23 to 74 years, with an average age of 55 years. All of these patients had been on prior antihypertensive treatment and had been followed from 6 to 48 months in the hypertensive outpatient clinic. All but one of these patients had required rauwolfia plus mecamylamine in their prior treatment program; the average maximum maintenance dosage of mecamylamine had been 27 mg. During therapy with rauwolfia plus mecamylamine, these patients had average recumbent and upright blood pressures of 200/110 and 170/100 mm. Hg, respectively. Before treatment with rauwolfia and mecamylamine, and after withdrawal of this treatment for 3 to 7 days, the average recumbent and upright blood pressures of this group were 220/140 and 200/130 mm. Hg, respectively. The current studies were made after withdrawal of all previous antihypertensive medication and the stabilization of blood pressure for a period of 3 to 7 days. Blood urea nitrogen determinations were within normal limits, and urinalyses were negative. None of the patients was in congestive heart failure, and in none of them did the fundoscopic hypertensive classification exceed Grade 2 (Keith-Wagener classification). The method of study has been described previously.[1]

RESULTS

Dose-Response Curves.—The single dose of S.9-390 necessary to produce a significant decrease in upright blood pressure (20 mm. of mercury mean blood pressure) was found to vary among individuals. This variation in dose response

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*2-(o-chlorobenzyl) imidazoline hydrochloride. Supplied by Dr. Melville Sahyun, Sahyun Laboratories, Santa Barbara, Calif.

was not a function of the patient's weight, nor of the degree of existing hypertension. The time of onset of blood pressure response, the duration of activity, and the degree of response of mean blood pressure were also found to vary in the individual patients, as observed in Table I. The degree of response was not a function of the size of the dose given, nor of the degree of pre-existing hypertension. There was no significant change in pulse rate.

TABLE I. THE ACUTE EFFECT OF S.9-390 ON BLOOD PRESSURE IN MAN

PATIENT	DOSE (MG.)	CONTROL*					DRUG†					ONSET‡ (MIN.)	DURATION§ (MIN.)
		R		U		MBP	R		U		MBP		
		S	D	S	D	U	S	D	S	D	U		
1. G.P.	12.5	220	146	230	140	170	180	120	100	80	87	90	240
2. S.J.	12.5	220	140	190	134	153	166	110	110	90	97	30	270
3. D.B.	25.0	230	146	200	140	160	150	110	90	70	77	30	360
4. J.W.	100.0	220	142	210	120	150	190	110	110	40	63	120	480
5. H.S.	12.5	216	134	176	128	144	140	110	120	60	80	30	360
6. S.L.	50.0	210	152	196	124	148	190	120	180	90	120	60	360
7. W.W.	100.0	234	130	200	124	149	166	100	100	80	87	120	480
8. J.H.	37.5	214	132	210	120	150	190	100	140	80	100	60	360
9. M.W.	12.5	216	142	208	140	163	170	110	130	80	97	30	300
10. C.S.	100.0	220	136	180	130	148	160	100	120	90	100	120	480
Average	46.25	220	140	200	130	154	170	109	120	76	91	69	369
P value											<.001		

*Average of 4 consecutive 15-minute periods.

†Maximum effect.

‡Time from administration of drug to the time when mean blood pressure decreases at least 20 mm. Hg in the upright position.

§Time from "onset" to point when mean blood pressure returns above a 20 mm. Hg reduction from control.

R = Recumbent. U = Upright. S = Systolic. D = Diastolic. MBP = Mean Blood Pressure.

Effects of Intravenous Norepinephrine.—In each of 5 patients tested, the upright blood pressure reduction produced by S.9-390 was reversed by the intravenous administration of norepinephrine in the dosage of 4 c.c./1,000 c.c. 5 per cent dextrose, given at a rate of 1.0 c.c. per minute, suggesting that the hypotensive effect due to the drug was not produced by sympathetic blockade.

Chronic Blood Pressure Response.—The chronic response of blood pressure to the administration of S.9-390 is summarized in Fig. 1. It can be seen that initially the response of the blood pressure to small doses of S.9-390 was significant. This response was consistently maintained throughout a 24-hour period when the drug was administered 4 times daily. However, in subsequent weeks of observation, the blood pressure showed a definite rise despite marked increase in dose. This still represented considerable improvement ($P<.001$, highly significant) over pretreatment levels, but seemed to indicate the development of drug resistance.

Effects of Addition of Chlorothiazide.—During the final 2 weeks of observation, chlorothiazide orally, 500 mg. twice daily, was added to the regimen in order to ascertain whether the hypotensive effects of a constant dose of S.9-390 might be augmented. Although some effect was produced (Fig. 1), the degree of augmentation was not as marked as had been noted previously when chlorothiazide was added to mecamylamine and/or rauwolfia therapy.[2,3]

Thus, the initial dose-response curves and observations of sleepiness, postural hypotension, and reversal of effects by intravenous norepinephrine suggest that S.9-390 acts both centrally and as a ganglionic blocking agent. In the human subject it did not appear to be sympatholytic in the dosage given. With continued administration there is a marked diminution in the degree of postural hypotension produced, the drug then appearing to have the characteristics of a centrally acting antihypertensive agent.

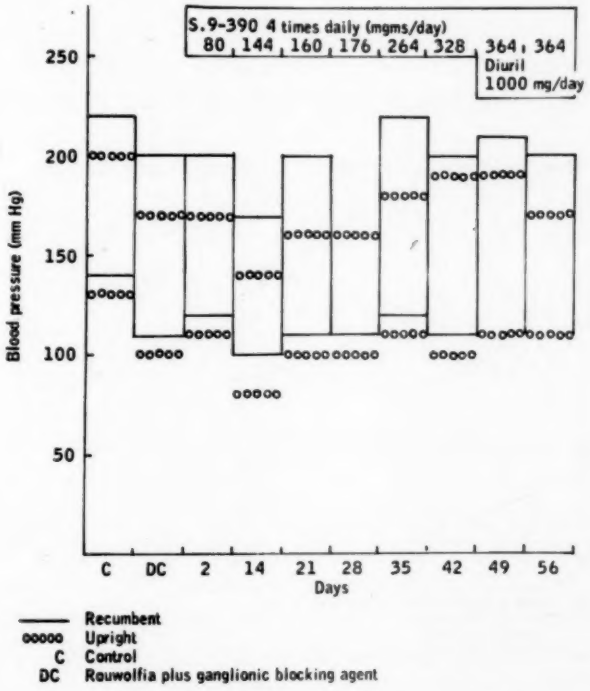

Fig. 1.—The consistency of effect of S.9-390 on blood pressure for 8 weeks (averages of 10 patients).

Toxicity.—Five of the 10 patients tested developed symptoms of postural hypotension during the first 2 to 4 days of drug administration. All of the patients were convinced, however, that there was significantly less postural dizziness than had been experienced with mecamylamine, especially after the first week of therapy. Seven of the 10 patients said they felt relaxed and sleepy while taking the drug, but were easily aroused to full consciousness and demonstrated no evidence of stupor, incoordination, nor slowness of motor or vocal response. Five of the 10 patients were gainfully employed in occupations requiring an average

amount of walking and standing. None of these patients felt that the drowsiness or postural dizziness was of significant degree to interfere with their effectiveness at work.

Other than these, no deleterious side effects were observed. There was no anorexia, vomiting, diarrhea, constipation, nor other evidence of gastrointestinal dysfunction or irritation. Again, all of the patients felt that there was noticeable absence of constipation, which had frequently been a problem while taking mecamylamine.

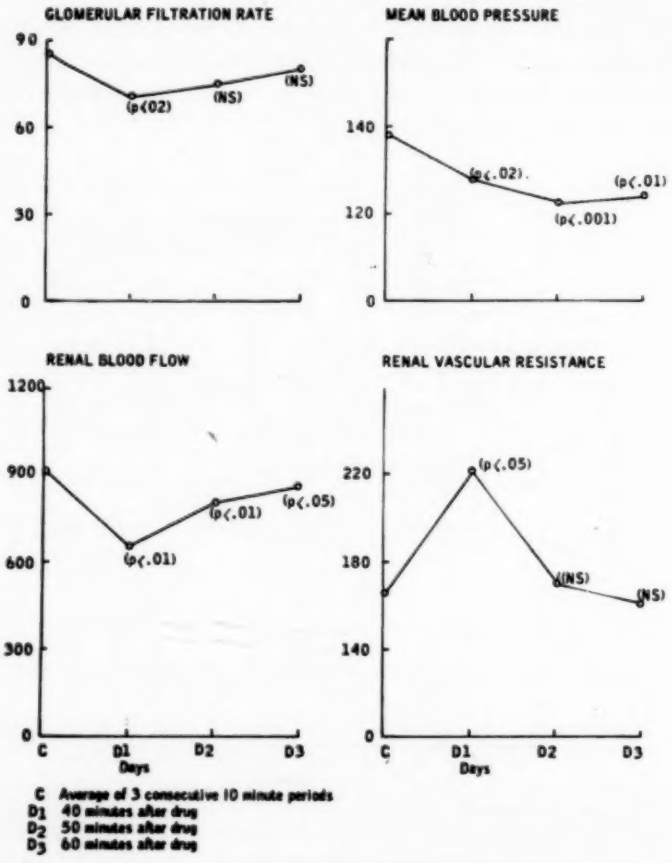

Fig. 2.—The effect of S.9-390, orally administered, on renal hemodynamics.

Routine studies of the hemogram, blood urea nitrogen, cephalin cholesterol flocculation, and urinalysis showed no appreciable change after 6 weeks of maintenance therapy with S.9-390. Routine evaluation, including physical examination and questioning, on follow-up visits did not indicate the presence of toxic effects other than those mentioned. There was no significant change in weight nor in the cardiovascular status of the patients during this period of observation.

Renal Hemodynamics.—Discrete renal function studies were measured prior to, and during, blood pressure reduction with S.9-390 in 5 hypertensive patients. The results of these studies are summarized in Fig. 2. Mean blood pressure in

these patients was progressively reduced. The glomerular filtration rate was transiently reduced but returned toward control before 60 minutes had elapsed. A similar change was observed in the calculated renal blood flow.

Calculations of renal vascular resistance (mean blood pressure × 1,000/renal blood flow) during this period show that initially there had been a rise which within 60 minutes decreased to a level actually slightly lower than the control value. These studies indicate a short-lived decrease in renal function. Further determinations indicated that while blood pressure reduction continues, renal function rapidly returns to near control levels within 20 minutes, because of a decreased renal vascular resistance. This is an additional contrasting feature between S.9-390 and the typical adrenergic blocking agent.

DISCUSSION

The need continues for effective, nontoxic, oral antihypertensive agents. In recent years, great strides have been made in the treatment of hypertension. In other laboratories,[4] animal investigations of S.9-390 (Fig. 3) have been conducted. In general, these indicated that the drug produced adrenolytic activity.

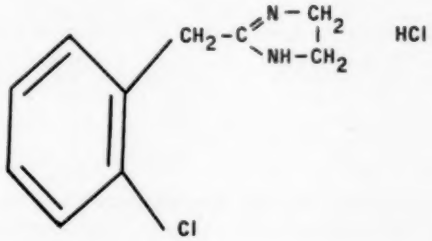

Fig. 3.—Structural formula of S.9-390 (2-(o-chlorobenzyl) imidazoline hydrochloride).

However, in our observations in man the drug presents the pharmacologic features of a ganglionic blocking agent, with some central activity manifested by the slight drowsiness it produces. There was no evidence of sympatholytic properties observed. The drug was found to be quite potent during the initial 2 weeks of therapy, with blood pressure control equal to that of combined mecamylamine and rauwolfia therapy. However, during the subsequent 6 weeks of observation there was a progressive diminution in the antihypertensive effect despite a fourfold increase in drug dosage, suggesting the development of resistance. A moderate augmentation of the antihypertensive effect was demonstrated during the last 2 weeks of investigation when chlorothiazide was added to the therapeutic program. Toxicity of the drug was minimal, the only protracted side effect being a slight tendency to drowsiness. Renal function studies before and during administration of S.9-390 were indicative of a transient decrease in renal function, which returned to near normal levels within a few minutes, although the antihypertensive effect persisted. Signs and symptoms of ganglionic blockade were less than those observed with combined rauwolfia and mecamylamine therapy, suggesting a slight central antihypertensive activity.

Thus, this drug, S.9-390, with its differing chemical structure, represents a new approach in the search for effective antihypertensive agents. Although this drug leaves something to be desired, it at least furnishes a stimulus to additional exploration of synthetic chemicals.

SUMMARY

The evaluation of a new, orally active antihypertensive agent, S.9-390 (2-(o-chlorobenzyl) imidazoline hydrochloride), has been presented. In human beings, the drug was found to have effects suggesting both central antihypertensive and ganglionic blocking action, but no characteristic adrenolytic properties. Although toxicity was minimal, the development of drug resistance prohibits its wide clinical use in hypertensive disease. It presents, however, many desirable features of an antihypertensive agent, so that further clinical studies in this field are warranted.

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ADDENDUM

Subsequent to our investigation, we had the opportunity to restart the administration of S.9-390 to patients who had developed a tolerance to it. The hypotensive effect appeared to be equal to that demonstrated when the drug was first used, suggesting a transient resistance.

Review

Some Aspects of the Role of Noradrenaline and Adrenaline in Circulation

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In its capacity of vasomotor and cardiac neurotransmitter noradrenaline exerts a profound influence on a variety of functions determining the integrated cardiovascular activity under normal as well as pathologic conditions. In this respect it differs from adrenaline which serves as an emergency hormone capable of modifying the circulation during special situations.

While the noradrenaline secreted from the adrenal medulla under conditions of circulatory stress may effectively support the vasomotor activity and, thus, take part in the sympatho-adrenal system, this secretion is normally of secondary importance as evidenced by the relatively undisturbed circulatory homeostasis after adrenalectomy. Exclusion of the adrenergic vasomotor regulatory system, on the other hand, occasioned either by ganglionic blocking agents, by sympatholytics, by extensive sympathectomy, or by pathologic changes as in postural hypotension, causes profound changes and overturns the circulatory homeostasis in standing, during muscular work, etc.

The difference in action between noradrenaline and adrenaline has not always been properly recognized and has sometimes led to complications in the therapeutic use of the drugs. The functional differentiation between the two hormones is, however, clearly established by recent research work and is further illuminated by their independent secretion from the adrenal medulla (cf. Euler,[16] p. 169).

In the following, some of the circulatory functions of noradrenaline will be reviewed briefly and compared with those of adrenaline.

The effects of adrenaline and noradrenaline on the heart are in many respects similar. Both hormones increase the rate of the isolated or denervated heart[11] and increase the force of the heart beat[10] (Fig. 1). The similarity of the actions must not obscure the differences, however. Thus, adrenaline seems to be more effective than noradrenaline in stimulating the heart muscle directly, as indicated by the observations of Nathanson and Miller[37] on the influence of these hormones on the heart rate in complete heart block. During these conditions adrenaline causes a marked increase in heart rate, while noradrenaline is without effect. These observations seem to indicate that the action of noradrenaline is chiefly on the pacemaker system.

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On the innervated heart noradrenaline causes reflex bradycardia, while adrenaline still causes a tachycardia. The mode of action of noradrenaline on the heart is further brought to light by the studies of Rushmer and West,[40] who found that infusion of 0.4 μg per kilogram per minute in the intact dog has only slight effect on the ventricular function, while exclusion of the reflex actions by tetraethylammonium chloride (TEAC) in a dose of 10 mg. per kilogram causes a marked increase in systolic pressure, stroke excursion, peak power, and cumulative stroke work.

The effect of the catechols on the oxygen consumption of the heart in relation to performance is not well known, but it appears probable that oxygen consumption is more enhanced by adrenaline than by noradrenaline, since the latter hormone has only little effect in general on metabolic processes, while adrenaline is a relatively efficient stimulator.

A problem of considerable interest is the action of the catechol hormones on the coronary flow. According to Wiggers,[46] even small doses of adrenaline increase the coronary vascular resistance, which means that the increased coronary flow after adrenaline is due to the greater force of ventricular contraction. Direct observations on isolated coronary vessels have shown vasodilatation after noradrenaline,[45] while adrenaline in larger doses constricts the vessels.

The normal vasomotor activity in the coronary vessels seems to be mediated by noradrenaline, as judged by the presence of considerable amounts of the neurotransmitter in extracts of these vessels.[42] It has been claimed that vasodilator substances appear in connection with the activity of the heart, but Jelliffe and associates[31] failed to find any indication of such effects when the coronary blood from an activated heart was circulated through the coronary vascular system of another heart.

A very marked difference between the effect of the two catechol hormones is observed on the cardiac output. Thus, it has been shown by Goldenberg and associates[23] and by several other workers that noradrenaline hardly influences the cardiac output in man, while adrenaline, as shown by Euler and Liljestrand[19] and many others, considerably increases the cardiac output. In animals the effects are more variable, but it seems fairly well established that, in the dog, small and moderate doses (0.5 μg/Kg./min.) of noradrenaline have no effect, while larger doses increase the cardiac output. The rise in cardiac output after adrenaline is ascribed to the increased venous return in consequence of vasoconstriction and an increased pressure gradient over the circulatory system.[25]

The effect of adrenaline and noradrenaline on the distribution of blood in the vascular system has been subjected recently to more detailed studies. If the left heart of the dog is replaced by a pump and a reservoir, the administration of noradrenaline results in a constriction of the total vascular bed and, consequently, an increased filling of the reservoir. A reduction of the total vascular volume by an average of 12 per cent was observed, and this was accompanied by an increased venous return and increased cardiac output.[39] In the intact animal the vasoconstriction is not followed by a change in the total vascular volume, owing to the incompressibility of the blood, but causes a marked shift in the blood distribution from the peripheral parts to the central parts: the lungs,

the large veins, and the right auricle.[44] An increase in heart volume during infusion of adrenaline was observed by Hamilton and associates[27] with the aid of x-ray measurements. Apparently the peripheral vasoconstriction causes a transfer of blood to the central distensible areas, thereby increasing the central blood volume.

The recent study by Levy,[34] in which the flow through a perfused hindleg of the dog is related to the arteriovenous pressure gradient, caused either by reduced arterial or by increased venous pressure, probably bears significant relationships to the effects of the catechol hormones. It is assumed that the different pressure gradient versus flow curves depends on the site of the distensible elements within the vascular bed. The results may be explained by postulating that the resistance vessels on the arterial side of the mid-point of resistance are in some part relatively distensible, while the venous vessels are less affected.

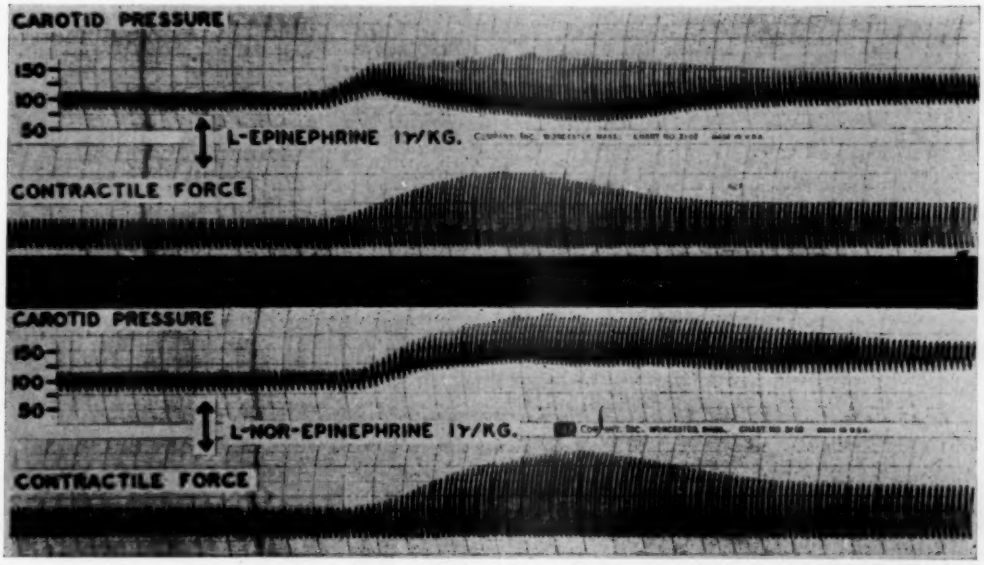

Fig. 1.—Synchronous oscillographic tracings demonstrating the effects of l-epinephrine and l-norepinephrine on blood pressure, ventricular contractile force, and heart rate in an anesthetized and vagotomized open-chest dog. The interval between two consecutive heavy vertical lines equals 2 seconds. (Cotten and Pincus,[10] Fig. 4.)

This assumption is supported by the observations of Pappenheimer and Soto-Rivera[38] that precapillary resistance is markedly altered by changes in perfusion pressure, whereas the postcapillary resistance remains constant. Changes in these conditions brought about by catechol hormones or vasomotor activity are obviously important for the blood flow in various regions. In this connection it may be relevant to recall the findings of Haddy, Fleishman and Emanuel[26] that while both adrenaline and noradrenaline in small doses constrict the small vessels of the isolated perfused foreleg of the dog, noradrenaline also constricts larger arteries and veins.

The effect of catechol amines on the distensibility of capacity vessels of the

hand and forearm in man has recently been studied by Glover, Greenfield, Kidd and Whelan.[22] The catechol amines were infused in doses of 0.1, 0.4, and 1.0 μg of the base per minute intra-arterially. A reduction in the resting volume, indicating a decrease mainly in the content of the high pressure capacity vessels, was observed at all dose levels. At varying degrees of venous congestion the increase in volume was reduced considerably, showing that the volume of the low-pressure capacity vessels (veins) was markedly diminished. With increasing doses the effects became augmented. It is interesting to note that the effects were qualitatively similar for adrenaline and noradrenaline, although the resistance to distention for a given dose was considerably greater with noradrenaline than with adrenaline. In earlier studies by Barcroft, Gaskell, Shepherd and Whelan,[4] it was shown that noradrenaline in a dose of 0.1 μg per minute decreased the blood flow in the hand and forearm to one third, while adrenaline in the same dose had a very slight effect.

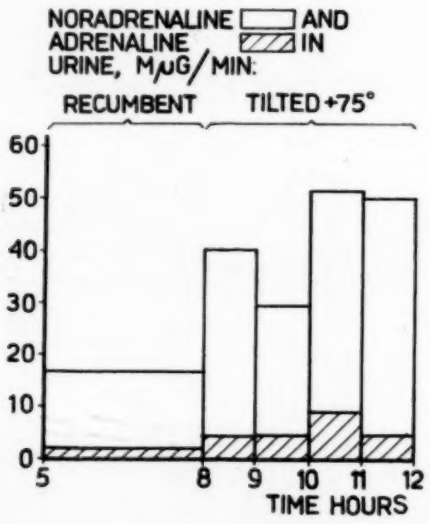

Fig. 2.—Effect of tilting +75 degrees on the urinary excretion of adrenaline and noradrenaline in a healthy subject. Ordinate: mμg/min. Abscissa: time in hours.

The general blood pressure is very differently influenced by adrenaline and noradrenaline. Thus, adrenaline in the physiologic dose range causes only very slight changes in the mean arterial pressure in man, whereas noradrenaline raises both the systolic and the diastolic pressures, and thus the mean pressure, as first demonstrated by Goldenberg[23] and subsequently confirmed by many investigators. In view of unchanged cardiac output the conclusion was drawn that noradrenaline produces a rise in the total peripheral resistance, in contradistinction to adrenaline which lowers it, as emphasized earlier.[19] The results furnish important data as to the interpretation of the relationships between vascular resistance, blood pressure, and cardiac output. Obviously, the increase in resistance is just compensated for by the rise in blood pressure so as to maintain an unchanged flow. The unchanged pressure head during adrenaline action, on the other hand, allows an increased flow through some dilated vascular areas.

The importance of noradrenaline for normal blood pressure homeostasis is illustrated by the reduced excretion of noradrenaline in patients with postural hypotension,[35a] as well as by the increased excretion when a subject is changed from recumbent to standing posture (Fig. 2).

Attempts to correlate essential hypertension to an increased endogenous release of noradrenaline have failed. On the contrary, the urinary excretion of noradrenaline in selected cases of essential hypertension is lower than normal, probably owing to reflex inhibition of the vasomotor system[7] (Fig. 3).

Green and co-workers have compared the effects of vasomotor nerve stimulation and the actions of adrenaline and noradrenaline on different vascular areas, and they also studied the influence of antiadrenalines on these effects. The blocking effects of Ilidar in increasing doses were similar for splanchnic stimulation and noradrenaline, which supports the conclusion that the mediator of the vasoconstrictor nerves is noradrenaline in the splanchnic bed in the dog.[13] The resistance was about equal in the small intestine and in the liver, indicating that the two vascular beds are innervated by the splanchnic nerves to a similar extent.

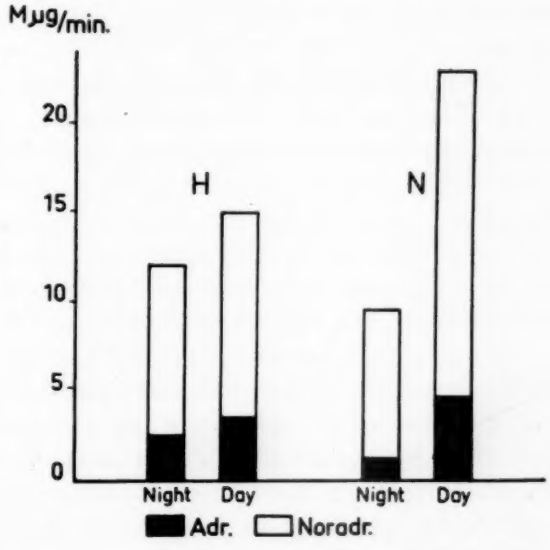

Fig. 3.—Catechol amine excretion in mμg per minute during the day (7 A.M. to 7 P.M.) and during night hours in patients with essential hypertension (*H*) and in healthy subjects (*N*). Patients were ambulatory during day hours. (Birke and associates.[7])

Several vascular regions respond very differently to adrenaline and noradrenaline, while others behave in a similar way. The most spectacular difference in the vascular response seems to be found in the skeletal muscle. As observed by Allen, Barcroft and Edholm,[1] infusion of adrenaline in man in a moderate dose increases the blood flow in the forearm to about twice the control value. This very marked and persistent effect is not seen with noradrenaline, which either slightly reduces the flow or slightly increases it as a result of the greater pressure head.[5] The dilatation of the vascular bed following the administration of adrenaline has been ascribed to the metabolic action of adrenaline, particularly

the increased formation of lactic acid[36] which is known to produce vasodilatation. Noradrenaline, on the other hand, has only a very slight action on the production of lactic acid. According to Lundholm, adrenaline, by virtue of its enhancing effect on the formation of lactic acid, efficiently increases the oxygen supply to the skeletal muscle, which is in line with its recognized role as an emergency hormone.

Less clear is the influence of the catechol hormones on the hepatic vessels. In isolated perfused livers the effect of catechol hormones is usually vasoconstriction, but in experiments on man both Bradley[9] and Bearn, Billing and Sherlock[6] found that adrenaline increases the flow. The latter authors observed very little change in the hepatic blood flow on infusion of noradrenaline. Similar results were obtained for the splanchnic blood flow in the dog by Farrand, Larsen and Horvath.[21] When adrenaline and noradrenaline were infused separately through the hepatic artery and the portal vein in the dog at a rate of 3 and 1 μg per minute, respectively, no change in blood flow was observed.[2] Since both amines were found to decrease the extraction rate of Bromsulphalein without changing the actually measured flow, the results obtained with the Bromsulphalein method seem to require reconsideration.

Both adrenaline and noradrenaline constrict the pulmonary vessels in the perfused lung,[3] but in the intact animal the response depends, to a large extent, on the pulmonary flow. Thus, an increase in the pulmonary arterial blood pressure after administration of catechol hormones may be associated with either a decreased or an increased pulmonary arterial resistance, depending on the cardiac output.[29] It is generally agreed that the pulmonary vessels are relatively insensitive to the action of the catechol hormones, just as they show a fairly poor response to vasomotor activation.[12] This is intelligible in view of their role of a dependent variable in the vascular system, being connected in series with the systemic flow. The very limited vasomotor supply to the small pulmonary vessels is reflected in the low content of neurotransmitter in the peripheral parts of the lungs. Thus, the lungs contain only about one hundredth of the amount of vasomotor transmitter present in the splenic tissue.[20]

A low sensitivity to the catechol hormones is also reported for the cerebral vessels. Sensenbach and associates[43] noticed vasoconstriction with noradrenaline but not with adrenaline. When all extracerebral vessels were excluded, neither of the hormones was found to have an action on the cerebral vessels.[24] On the other hand, Bovet and associates[8] noticed a pressure drop in the cerebral veins after injection of adrenaline and noradrenaline, and concluded that the two hormones constricted cerebral vessels. They ascribed the failure of some authors to observe these changes to the fact that the sensitivity of the brain vessels was readily abolished by barbiturate anesthesia, respiratory acidosis, and shocklike conditions. As in the lungs the vasomotor supply to the cerebral vessels is sparse, as judged by the catechol content of the brain tissue.[16]

Similar actions of adrenaline and noradrenaline have been reported repeatedly for the renal circulation. Handley and Moyer[28] observed that low rates of infusion of both adrenaline and noradrenaline caused increased diuresis as a result of an increased glomerular filtration rate, while higher infusion rates often

reduced the renal output. When the arterial blood pressure was maintained at a constant level, the only effect of adrenaline, in dogs under spinal anesthesia, was a reduction of the urine flow, owing to vascular constriction. In contrast to this finding the diuresis increased when the blood pressure was allowed to rise. This suggests that the increase in blood pressure normally compensates for the vasoconstriction. When the infusion rate of noradrenaline was 0.8 μg per kilogram per minute, the urine flow showed a maximum, and fell during higher infusion rates.[33] The arterial blood pressure showed a similar course for both hormones during these conditions.

The vessels of the skin react, as a rule, more strongly to adrenaline than to noradrenaline. The relative degree of vasoconstriction varies somewhat in different studies, but generally the response to noradrenaline is reported to be about one half to one third of that of adrenaline. Schiller,[41] in a recent study, found adrenaline 3 times more efficient as a vasoconstrictor for the skin vessels than noradrenaline. These observations agree with the findings of several investigators as regards the ability of the two hormones to prolong local anesthesia. Thus, Ekmanner and Persson[15] found that noradrenaline 1:60,000, together with lidocaine, had a somewhat less prolonging effect on mandibular and terminal anesthesia than did adrenaline 1:80,000. A marked prolongation of the duration of spinal anesthesia was shown by Liljedahl[35] to occur when 0.5 mg. of noradrenaline was added to 20 mg. of Pontocaine intrathecally.

The therapeutic implications of the different properties of adrenaline and noradrenaline are in many respects self-evident. There is good experimental evidence that noradrenaline is released in the body in conditions which primarily required support for the blood pressure homeostasis. Thus, the change in position from recumbent to standing is accompanied by a large release of noradrenaline, as evidenced by the increased urinary output. This effect is mediated chiefly by the vasomotor nerves, since a similar increase in the urinary output of noradrenaline was found also in adrenalectomized patients on tilting.[17] However, an increased secretion from the noradrenaline-producing cells in the suprarenal medulla[30] can be demonstrated also on lowering the intrasinusal pressure.[32] Adrenaline is not released to any considerable extent during such conditions but is secreted during conditions of physiologic and mental stress. The large increase in the output of the catechol amines during strenuous muscular work is probably a sign of activation of the homeostatic mechanisms.[18] The selective release of adrenaline during hypoglycemia is in accord with the stimulating effect on glycogenolysis of adrenaline, an action which is very weak for noradrenaline.

The use of noradrenaline as a means of raising the systemic blood pressure during hypotension of varying origin has become widely adopted, and has the advantage over the use of other drugs of being strictly physiologic. The efficiency of noradrenaline is particularly marked in situations of circulatory insufficiency due to reflex vasodilatation, cardiac hypoactivity, or after exclusion of the central vasomotor tone, provided that the reactivity of the vessels is not greatly diminished. If the vascular response to intense vasomotor activity is poor, the response to exogenously administered noradrenaline or similarly acting drugs is probably also unsatisfactory.

It has been observed both clinically and in animal experiments that during prolonged infusion of noradrenaline the blood pressure tends to fall, and that after conclusion of the infusion an abrupt drop may occur, often necessitating resumed infusion. This effect was studied by Dunér and Euler,[14] who found that the prolonged afterfall could be largely prevented by the previous administration of TEA (tetraethylammonium chloride).

Although the actions of noradrenaline have been partly elucidated by clinical and laboratory research during recent years, many points still require further study. The effects of noradrenaline on the total blood flow during various pathologic conditions, particularly in different kinds of shock, is still largely obscure. Likewise, the conditions during which noradrenaline increases the efficiency of the heart during coronary occlusion is in need of further study. Although the role of noradrenaline as a physiologic regulator of the blood pressure level is well established, possible other functions, among others relating to actions on the central nervous system, should not be forgotten.

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Book Review

DIE NEUZEITLICHEN BRUSTWAND UND EXTREMITÄTEN—ABLEITUNGEN IN DER PRAXIS. By Herbert Reindell and Helmut Klepzig, Stuttgart, 1958, Georg Thieme Verlag, 192 pages, 82 illustrations.

In view of the present search for new electrocardiographic leads which have less distortion than the conventional leads, one perhaps might expect, from the title, some information about their practical application. However, as stated in the preface by L. Heilmeyer, the main purpose of the book is a condensed presentation of the large "Anglo-American" literature on Wilson's V-leads (proposed 20 years ago) and Goldberger's aV-leads (proposed 15 years ago); these are critically discussed on the basis of the authors' own material. Since these leads were introduced into general use in Germany much later, the title may be justified for the average German reader.

Actually, the book gives more than that. Vectorcardiographic information is integrated, and also chest leads, in addition to Leads V_1-V_6, and esophageal leads are considered in the discussion, together, of course, with the standard leads which are still the basis of clinical electrocardiography.

The book is fluently written and gives, in a comparatively small volume, up-to-date and adequate information on the clinical use of the 12-lead ECG. Arrhythmias are not included; indeed, the contribution of the V-leads to the differentiation of arrhythmias is small.

The book is quite similar to most recent electrocardiographic textbooks. A distinguishing feature is the relatively large space devoted to the normal electrocardiogram (pages 22-52). The recognition of the importance of normal variations is certainly to the credit of the authors, but their treatment of normal variations is open to criticism.

The authors present the normal standards for the V-leads from their own material of 100 cardiac normals ("Herzgesunden") and 40 trained subjects. The composition of the "normal" group (age, body weight, sex) is not given, but it is probably a heterogeneous group, and the specification of absent cardiac pathology suggests that patients with other types of pathology may have been included. "Standards" derived from such groups can, at best, give only a preliminary orientation. It cannot be expected that such standards could be reproduced in another group of different composition. Indeed, the authors find that their values differ from those of Sokolov and Friedlander. They suggest that these differences are, in the first place, due to a different nutritional state between theirs and Sokolov's group, which is not supported by actual evidence; most likely, other uncontrolled constitutional factors were more important. Sokolov and Friedlander's group was also heterogeneous, and group differences should be expected when two heterogeneous groups are compared. Similarly, the fact that the voltage of deflections in the group of 40 trained subjects was higher than that in the 100 "normal" subjects may be due to a different age or sex composition of the two groups rather than to training. It should be said, however, that the treatment of normal variations is also not adequate in some other recent textbooks of electrocardiography.

The book is recommended as a critical evaluation of the present 12-lead electrocardiography, written from a large clinical experience of the authors. It is illustrated by a great number of excellent figures and diagrams.

E. S.